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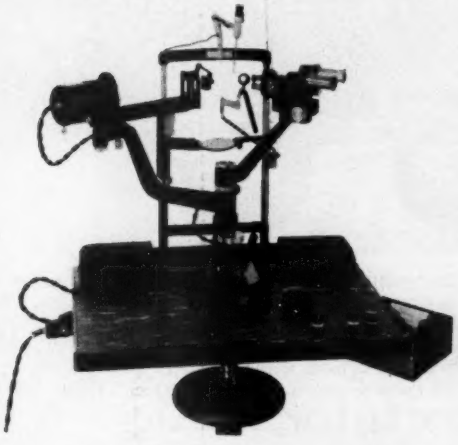

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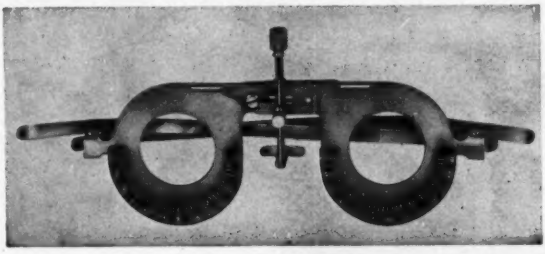

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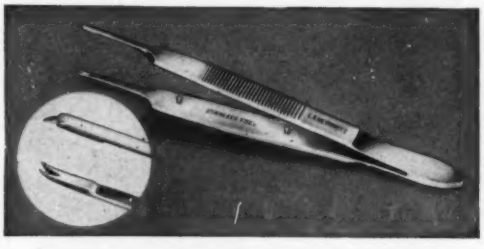

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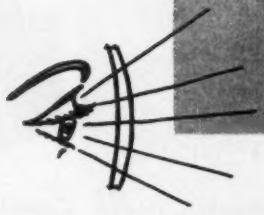

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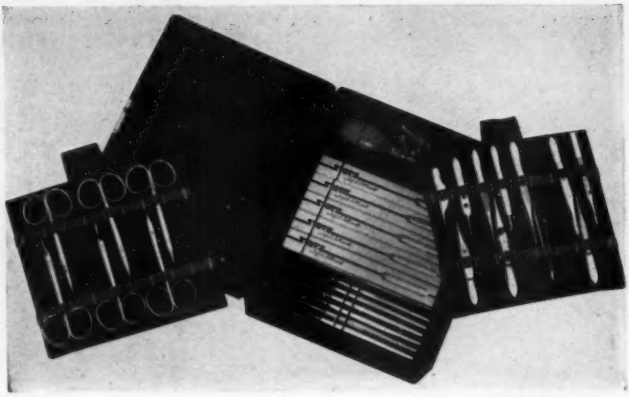

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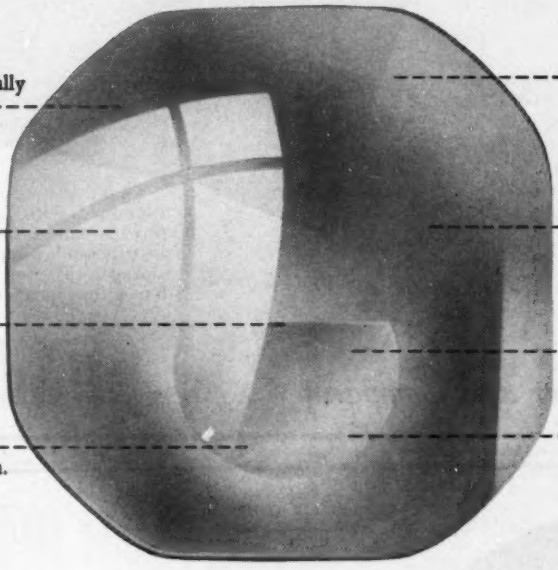
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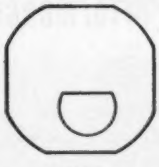

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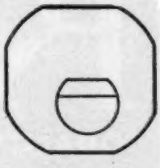

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|---|---|---|---|
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Assume patient reads normally at 7 mm. below optical center of distance lens (4 mm. below segment top).

| | | | |
|---|---|---|---|
| *Then:* | $\frac{+4.00 \times 7}{10}$ | = | **2.8△ B.U.** |
| | $\frac{+1.00 \times 7}{10}$ | = | **.7△ B.U.** |
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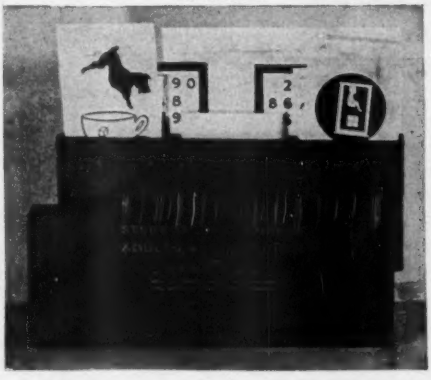

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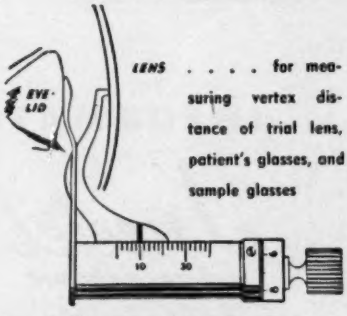


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# BILATERAL TRANSVERSE OPTIC NEURITIS

## Report of Two Cases with Cortisone Therapy

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SUDDEN binocular blindness occurring in an apparently healthy patient for no obvious reason is, fortunately, unusual. The purpose of this paper is to report on two such patients who were recently treated with cortisone and to discuss the diagnostic possibilities presented.

### PRESENTATION OF CASES

CASE 1.—E. L., a white man aged 30, an athletic coach, was admitted to the Veterans Administration Hospital, Jefferson Barracks, Mo., on June 18, 1950. At that time, he had been completely blind in both eyes for 24 hr.

*History.*—On May 21, 1950, he received penicillin because of a "fever and sore throat." One week later vision was blurred in the left eye but then improved, and he was asymptomatic until June 15, when vision began to fail in both eyes and within two days had progressed to complete blindness. He had also experienced recent difficulty in urinating.

Past and family histories were noncontributory.

*Physical Examination.*—The pupils were widely dilated and fixed to light. There was no light perception in either eye, and funduscopic examination revealed hyperemia and edema of both disks, with an elevation of 2 D. There was no nystagmus, and the extraocular muscles appeared to function normally.

Repeated neurological examinations gave normal findings until June 22, when the abdominal and cremasteric reflexes were found to be absent. There was also ankle clonus on the left, and the deep reflexes were hyperactive.

An electroencephalogram showed an arrhythmia of questionable significance.

*Laboratory Findings.*—On admission, the urea and sugar of the blood were within normal limits. The Kahn reaction was negative, and the urine was normal, but there was leucocytosis, with a count of 15,100 white blood cells per cubic millimeter. The spinal fluid was found to be under normal pressure. The laboratory reported 86 white blood cells per cubic millimeter, 98% of which were lymphocytes; 80 mg. of total protein per 100 cc.; a positive reaction for globulin; 58 mg. of glucose per 100 cc.; a colloidal gold curve of 0011000000; a negative Wassermann reaction, and absence of bacterial growth on culture. Blood serum tests for western equine encephalitis and epidemic (St. Louis) encephalitis gave negative results.

*X-Ray Examination.*—Initial therapy included use of nicotinic acid, thiamine hydrochloride, and therapeutic doses of vitamins. A tentative diagnosis of neuromyelitis optica (acute transverse myelitis with optic neuritis) was made, and on June 22 treatment with intramuscular injections of cortisone acetate, 100 mg. three times daily, and aureomycin, 0.5 gm. four times daily, was started. The dosage of cortisone was later reduced to 100 mg. two times a day on June 26 and then to 100 mg. daily on July 12.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

*Course in Hospital.*—Otolaryngologic consultation failed to reveal any foci of infection.

On June 20, the patient required catheterization, and a large amount of urine was obtained. Urethrocystoscopic examination revealed a spastic internal urethral sphincter.

There was an unexplained fever (temperature of 104 F.) on June 23, and the patient complained of a burning sensation over the skin of the lower portion of the abdomen and of both flanks. He also noticed that his left leg felt heavy and cold. However, his temperature was normal thereafter, and no further neurological symptoms were experienced.

On June 26, the pupils reacted slightly to light, and the patient could detect hand movements at 2 ft. (60 cm.) before either eye. Improvement continued, so that by July 6 the visual acuity of the right eye was 20/400, while that of the left was 20/25. On this date examination of the visual fields revealed concentric contraction bilaterally and a central scotoma on the right.

Funduscopic examination on July 14 disclosed a blurred disk on the right with an elevation of 1 D. The disk on the left was blurred only at its nasal margin, and slight temporal pallor was noted. Visual acuity on this date was 20/40 in the right eye and 20/30 in the left eye.

All therapy was discontinued on July 21, and the patient was kept under observation for 10 days before being sent home.

The spinal fluid on July 27 was entirely normal. Neurological examination prior to his discharge from the hospital disclosed hyperactive deep reflexes and a Babinski sign bilaterally. Repeated electroencephalograms had consistently shown an arrhythmia of questionable significance.

Reexamination on Sept. 25 found the patient asymptomatic and the visual acuity 20/30 in the right eye and 20/25 in the left eye. Both disks were pale, and there was sheathing of the vessels about the disks. The visual fields were normal except for slight concentric contraction.

When he was last observed on March 22, 1951, the patient was asymptomatic, and the visual acuity was 20/25 in each eye. The disks were pale and the arterioles moderately attenuated. The fields were only slightly contracted. Neurological examination at this time disclosed a Babinski sign on the left, Hoffmann sign on the right, and hyperactive deep reflexes. The impression of the neurological service at this time was that these findings represented the residual changes of neuromyelitis optica, or possibly the early changes of multiple sclerosis.

Case 2 (presented with the permission of Dr. T. E. Sanders).—M. F., a Negro laborer aged 18, was admitted to Barnes Hospital, St. Louis, on June 15, 1950, with a history of having first noticed blurred vision in the left eye three days previously. This eye had become totally blind within 24 hours, and the right eye had complete loss of vision on the following day.

The previous and family histories were noncontributory.

*Physical Examination.*—The physical condition was entirely normal except for the presence of widely dilated pupils, which did not react to light, and mild bilateral optic neuritis. There was no light perception in either eye.

Neurological examination disclosed no motor or sensory abnormality other than a lifelong speech defect, and there was questionable mental retardation. An electroencephalogram was normal.

*Laboratory Findings.*—The urine was normal; the Kahn test gave a negative reaction, and normal values were found for the sugar, nonprotein nitrogen, and cytologic constituents of the blood. Examination of the spinal fluid on June 16 revealed a normal pressure and normal values for total protein, the colloidal gold curve, and the cell count. The Wassermann reaction was negative.

*X-Ray Study.*—Roentgenograms of the skull, paranasal sinuses, and optic foramens revealed nothing abnormal.

*Treatment.*—Therapy consisted of the intramuscular injection of 100 mg. of cortisone three times a day, beginning June 16. This dose was reduced to 100 mg. twice daily on June 19, and cortisone therapy was discontinued on June 27.

*Course in Hospital.*—By June 18, three days after his admission, a slight pupillary response was elicited to light, and the following day there was perception of hand movements in each eye.

On June 20 vision was 20/200 (eccentrically) in the right eye and 5/200 (eccentrically) in the left eye. There was less edema of the disks, and the peripheral fields were fairly full; but there was a central scotoma bilaterally.

Two days later vision was 20/40 in each eye and the fundi appeared normal.

A spinal puncture on July 1 again revealed normal fluid, and the patient was discharged the following day with a visual acuity of 20/25 in each eye and with essentially normal fields and fundi. The diagnosis at that time was severe bilateral optic neuritis of undetermined origin.

A follow-up examination on July 24 disclosed vision of 20/25 in each eye with bilateral pallor of the disks. The patient had had no symptoms since his hospitalization, and he was told to return again in two months for reexamination but failed to do so.

## COMMENT

In the two cases presented it is not possible to make a conclusive diagnosis other than that of bilateral transverse optic neuritis.

One can but speculate as to what disease processes were present to have produced this clinical picture. Perhaps these features were only the first phase of what may subsequently reveal itself as a well-recognized syndrome.

The differential diagnosis, when such patients are seen in the acute stage, presents several possibilities.

Walsh and Ford [1] warned of the dangers in mistaking such a condition for cerebral neoplasm with increased intracranial pressure. The history of sudden complete, or near complete, loss of vision should preclude this error.

Focal infections and the so-called toxic disorders should be ruled out, although it is not likely that they could produce the clinical picture here presented.

The "demyelinating diseases" would seem to offer the most likely diagnosis. Included in this group are Schilder's disease (progressive subcortical encephalopathy), acute disseminated encephalomyelitis, multiple sclerosis, and neuromyelitis optica.

Berliner [2] stated the belief, as have many others, that these diseases may represent one and the same pathological process, differing only in their predilection for certain tissues.

That the two cases reported in this paper could represent either Schilder's disease or acute disseminated encephalomyelitis is highly improbable. Schilder's disease is characterized by sudden visual loss, a familial incidence, mental deterioration, normal pupils with cortical blindness, and death in a few months, while acute disseminated encephalomyelitis is said to follow vaccination or various virus infections, and, in addition to optic neuritis, there are prominent cerebral symptoms.

Multiple sclerosis must be considered in the differential diagnosis, but the occurence of complete bilateral loss of vision in this disease is practically unknown. Sarbo, cited by Duke-Elder,[3] in 1932, reported 600 cases of multiple sclerosis, in none of which there was complete blindness. The absence of nystagmus and paralyses of the extraocular muscles also makes disseminated sclerosis a less likely diagnosis.

Neuromyelitis optica was originally described by Devic in 1894 as a syndrome consisting of bilateral optic neuritis, accompanied with acute myelitis with paraplegia. It tends to be self-limiting and ends in death or recovery in a relatively

1. Walsh, F. B., and Ford, F. R.: Central Scotomas, Arch. Ophth. **24**:525 (Sept.) 1940.

2. Berliner, M.: Acute Optic Neuritis and Demyelinating Diseases of the Nervous System, Arch. Ophth. **13**:83 (Jan.) 1935.

3. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1940, Vol. 3, pp. 2993-2995.

short time. Its fatal termination is usually the result of ascending myelitis. The optic neuritis produced may be retrobulbar or in the papilla and is most commonly transverse.

Duke-Elder [3] writes that almost complete blindness and a widely dilated pupil are the rule, and Brain [4] states that sudden binocular loss of vision is almost pathognomonic of neuromyelitis optica, whereas it is rarely seen in multiple sclerosis.

During recovery, the peripheral fields are said to return first, so that central scotomas are produced.

Walsh [5] states that the spinal fluid usually shows 20 to 50 lymphocytes per cubic millimeter during the acute stages, but Stansbury,[6] in a recent review of the literature, concluded that there were no laboratory findings peculiar to the disease.

The etiology of neuromyelitis optica is still obscure, but the infectious theory remains a popular one and the toxic and allergic theories have not been disproved.

That the typical transverse optic neuritis of Devic's disease can occur without spinal cord symptoms has been suggested by Walsh [5] under what he describes as "abortive neuromyelitis optica." In his textbook,[5] he describes three cases of sudden bilateral loss of vision in which there were minimal or no signs of myelitis and in which good vision returned. These patients he followed for a number of years, and they remained asymptomatic.

It may be that the cases reported in this paper represent just such an "abortive neuromyelitis optica." It is also possible that the administration of cortisone to these patients may have been responsible for the arrest of the disease before myelitis developed. For this reason, the future use of cortisone would appear warranted in similar cases until such time as further evaluation can confirm or deny its value.

## SUMMARY

Two cases of severe transverse optic neuritis with bilateral blindness are presented. One patient had transient urinary retention and alteration of reflexes, suggestive of mild myelitis, while the second patient had no positive neurological signs at any time.

The diagnostic problems posed by this clinical picture are considered, and it is concluded that these cases may represent what has been called "abortive neuromyelitis optica."

Cortisone was administered in each case, and visual improvement was rapid. This improvement may have been coincidental, but justifies the use of cortisone in similar cases until it can be demonstrated whether or not cortisone was of benefit.

The part played by the administration of cortisone in limiting the progress of the disease is necessarily conjectural, and further evaluation of this drug in the treatment of similar conditions is required before any definite conclusions can be drawn. However, it is quite possible that a potent weapon is now available against a disease which has heretofore resisted all therapeutic measures.

4. Brain, W. R.: Critical Review: Disseminated Sclerosis, Quart. J. Med. **23**:343, 1930.

5. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, pp. 783-790.

6. Stansbury, F. C.: Neuromyelitis Optica (Devic's Disease), Arch. Ophth **42**:292 (Sept.) 1949.

# GENETICS OF RETINOBLASTOMA

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IT HAS been recognized for many years that the distribution of the malignant ocular neoplasm most commonly termed retinoblastoma is not at random in human populations. Although the great majority of persons with this disease are not known to have any relative similarly affected, there has been observed, considering the rarity of the neoplasm, a disproportionate frequency of both "horizontal" and "vertical" constellations. By the term "horizontal" we refer to the occurrence of two or more affected children in a single sibship, both parents being normal in this respect; by the term "vertical" we refer to an affected parent with one or more affected children. The extensive literature documenting this point has been adequately reviewed elsewhere.[1] The currently accepted genetic explanation of these findings is largely derived from the papers of Weller,[1b] Griffith and Sorsby,[1c] Franceschetti and Bischler,[1e] and Falls.[2] In brief, it is postulated that the development of a retinoblastoma is dependent upon the presence of a single dominant gene. The number of such genes present in a population is constantly being added to as a result of the appearance through mutation of new retinoblastoma genes, and is constantly being subtracted from because of the death of affected persons. In a state of nature, most retinoblastoma genes would be eliminated during the same generation in which they appeared, i. e., persons who manifested the disease in consequence of receiving a mutant gene from one or the other of their parents would generally not survive to reproduce. Occasionally, however, in consequence either of spontaneous regression of the tumor or of the ministrations of the ophthalmologist, persons with the disease do reproduce, in which case approximately half their children are affected (the "vertical" constellations). It is further postulated that, for reasons not now understood, not all persons who possess this particular gene

From the Department of Ophthalmology of the University Hospital and the Heredity Clinic of the Institute of Human Biology, University of Michigan.

1. (*a*) Benedict, W. L.: Retinoblastoma in Homologous Eyes of Identical Twins, Arch. Ophth. **2**:545 (Nov.) 1929. (*b*) Weller, C. V.: The Inheritance of Retinoblastoma and Its Relationship to Practical Eugenics, Cancer Res. **1**:517, 1941. (*c*) Griffith, A. D., and Sorsby, A.: The Genetics of Retinoblastoma, Brit. J. Ophth. **28**:279, 1944. (*d*) Rados, A.: Occurrence of Glioma of Retina and Brain in Collateral Lines in the Same Family: Genetics of Glioma, Arch. Ophth. **35**:1 (Jan.) 1946. (*e*) Franceschetti, A., and Bischler, V.: Rétinoblastome et hérédité, Arch. Julius Klaus-Stift. f. Vererbungsforsch. **21**:322, 1946.

2. Falls, H. F.: Inheritance of Retinoblastoma: Two Families Supplying Evidence, J. A. M. A. **133**:171 (Jan. 18) 1947.

manifest a retinoblastoma, a small proportion being assumed to appear clinically normal. These normal carriers, however, will still transmit the gene to half their children, who may be expected to manifest the disease—this accounts for the instances of "horizontal" constellations. Philip and Sorsby,[3] in an unpublished paper presented several years ago before the Genetical Society of Great Britain, estimated that in London the frequency with which this gene arises by mutation is $1.4 \times 10^{-5}$. That is to say, of 100,000 gametes, 1.4 will on the average, as a result of mutation, carry a newly arisen gene for retinoblastoma.

The present study constitutes a second attempt to estimate the rate of mutation for this gene. Furthermore, an attempt has been made to inquire into factors which may be related to this mutation rate, such as secular trends, parental age, general environment (urban versus rural), and occurrence of cancer in other members of the family. Recognition of the fundamental role of mutation in human biological processes and problems has been slow in coming (Muller[4]). Knowledge of the rate of mutation of specific human genes is still woefully deficient. Retinoblastoma, because of its clear-cut nature and striking effect, is unusually favorable material for studies of mutation rates. The fact that the rate of mutation of this gene has already been estimated by two English investigators was felt to be, if anything, an added incentive to this study, since the question of whether equal rates of mutation obtain in widely separated geographic areas is one that has broad biological consequences.

In addition, an attempt has been made in the present study to determine future trends in the incidence of this disease. As the proportion of five-year survivals increases, because of improving levels of pediatric and ophthalmological care, the relative number of affected persons who reproduce will increase, i. e., the proportion of cases represented by "vertical" distributions will be greater. Assuming a constant rate of mutation, this can only mean that the disease will become more frequent. Retinoblastoma is but one of a number of diseases in which the checks formerly imposed by natural selection are being removed. The findings with respect to this disease, accordingly, have a wide applicability.

## MATERIAL

Prerequisite to any attempt to estimate a mutation rate is the derivation of an accurate incidence figure. An attempt, therefore, was made to establish as complete a roster as possible of cases of retinoblastoma occurring in the State of Michigan from 1938 to 1947, inclusive. A first step in compiling such a roster was to locate as many certain or probable cases as could be found; the sources are as follows:

1. Records of the Heredity Clinic and the University Hospital of the University of Michigan (28 alleged cases).

2. Files of the office occupied jointly by Dr. F. Bruce Fralick, one of us (H. F. F.), and (prior to his death) Dr. Albert Barr (28 alleged cases).

3. Department of pathology of the University of Michigan, through the kindness of Dr. Carl V. Weller, who made available a list of all specimens of retinoblastoma referred to the department for diagnosis during the 10-yr. period under study (24 cases).

4. Correspondence with the 214 hospitals in the State of Michigan (other than the University Hospital) with a capacity of 10 beds or more, exclusive of private hospitals for the treatment of

3. Philip, U., and Sorsby, A.: The Mutation Rate of Retinoblastoma, unpublished manuscript presented before the Genetical Society of Great Britain, December, 1944.

4. Muller, H. J.: Our Load of Mutations, Am. J. Human Genetics **2**:111, 1950.

alcoholism or mental disease. A total of 147 of these hospitals answered a query concerning the admission of patients with retinoblastoma between 1938 and 1947, a "response rate" of 0.69, with information on 32 presumptive cases.

5. Correspondence with the 218 physicians in the State of Michigan listed by the department of ophthalmology of the Medical School as devoting all or a large portion of their time to the practice of ophthalmology. A total of 105 of these physicians replied to a letter of inquiry concerning the occurrence of retinoblastoma in their practices between 1938 and 1947; in 18 instances the letter was returned because the address was incorrect, and in 6 instances the letter was returned because the physician was dead. Exclusive of the latter two categories, the "response rate" was 0.54. Information was obtained in this fashion concerning 11 presumptive cases.

6. Department of Vital Statistics of the State of Michigan, which permitted us to examine those death certificates filed between 1943 and 1947 on which the primary cause was listed as cancer of the eye. There were 43 such certificates, on four of which there was a definite diagnosis of retinoblastoma. In 23 cases there was uncertainty concerning the exact histological diagnosis, and letters were written to the attending physician or the family to clarify this point. Ten of these were answered, with information concerning one more case. The total of cases located by this approach was thus five.

7. The Armed Forces Institute of Pathology, which examined its files for accessions of retinoblastoma originating in the State of Michigan and submitted to the Institute for diagnosis between 1938 and 1947. A record of one case was obtained in this manner.

8. A visit to the Michigan State School for the Blind in Lansing yielded the names of three children currently in attendance whose blindness was due to bilateral retinoblastoma.

9. A brief newspaper account of the investigation which resulted in two alleged cases of the disease being brought to our attention.

In consequence of investigation of these nine sources, a preliminary roster of 66 cases of retinoblastoma, representing 65 families, was established. Most of the names on the list were derived from at least two of the independent sources listed above, and some from three or four. A trained field worker then attempted to establish personal contact with each family and to obtain preliminary family and medical histories, including information on certain or probable cases of malignant growths in sibs, parents, grandparents, and uncles and aunts. It was possible, by utilizing all available channels, to trace all but one of these families. Once contact had been established, the propositus (if alive), his siblings, and his parents were interviewed personally by us, the interviews being carried out either at the Heredity Clinic or in the home. At this interview, the previously obtained data were verified; a more detailed medical history was obtained; ophthalmological examinations were carried out on as many members of the immediate family as possible, and, where circumstances permitted, a brief physical examination was also performed. As a result of these studies, 13 families were eliminated from the tentative list of retinoblastoma families, leaving 52 families, with 53 cases, for 48 of which pathological confirmation of the diagnosis was available. Of the five cases which have not been confirmed by a pathologist's report, in two the diagnosis is at least partially substantiated by the subsequent death of the child; in one the diagnosis was agreed to by four ophthalmologists; in one the diagnosis was verified for the child's identical twin sister, and in only one may the diagnosis be regarded as doubtful. Of the cases in the 13 families eliminated from the list, the correct diagnosis was thought to be retrolental fibroplasia in nine, melanosarcoma in two, amaurosis due to a defect of the central nervous system in one, and retinal detachment and gliosis with maldevelopment of the lens and organization of the vitreous in one.

Certain essential medical information concerning each of the families involved is presented in Table 1. Also presented in the table is information concerning 20 other cases of retinoblastoma originating later than 1947 which came to our attention during the course of this study. These cases, while they cannot be utilized in the derivation of frequency figures because they are not the result of an effort to locate *all* Michigan cases between 1948 and 1951, can, nevertheless, be utilized in some of the calculations to follow concerning the biology of the disease.

TABLE 1.—*Data on Seventy-Two Kindreds in Which One or More Cases of Retinoblastoma Have Occurred*

| Kindred No. | Year of Diagnosis | Sex of Patient | Age When Disease Was Noted by Parents, Mo. | Age When Patient Was First Seen by Physician, Mo. | Age at Definitive Treatment, Mo. | Age at Death (If Deceased), Yr. | Age When Last Examined (If Alive), Yr. | Affected Eye or Eyes | Pathological Confirmation of Diagnosis | No. of Normal Sibs (Living More than One Yr.) | Age of Father at Birth of Patient | Age of Mother at Birth of Patient | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1938 | F | 16 | 16 | 16 | .. | 13 | O. D. | + | 0 | 41 | 42 | ..... |
| 2 | 1938 | F | 12 | 12 | 12 | .. | 11½ | O. S. | + | See "Comment" | See "Comment" | See "Comment" | Father with retinoblastoma (O. S.); patient's only sibling (sister) with retinoblastoma (O. U.), with death at age 4½ yr., as reported by Weller [1b] (cf. our Fig. 1); paternal grandfather aged 30 and paternal grandmother aged 27 at father's birth |
| 3 | 1938 | F | 4 | 4 | 9 | .. | 12 | O. S. | + | 2 | 25½ | 26½ | ..... |
| 4 | 1939 | F | ? | 20 | 20 | 6 | .. | O. U. | + | See "Comment" | See "Comment" | See "Comment" | Five of 9 siblings manifested retinoblastoma, one with disease in O. D. and operation at age of 2 yr., living at age of 27; other 4 deceased, as reported by Weller [1b] and Falls (Am. J. Ophth. 25:42, 1942) (cf. our Fig. 1); father and mother, latter mentally retarded, ophthalmologically normal |
| 5 | 1939 | F | 5 | 15 | 18 | .. | 10½ | O. D. | + | 1 | 33½ | 30 | ..... |
| 6 | 1939 | M | 30 | 30 | 30 | .. | 12½ | O. S. | + | 1 | 22 | 20½ | ..... |
| 7 | 1939 | M | 34 | 34 | 40 | 3½ | .. | O. S. | + | 3 | 33½ | 23 | ..... |
| 8 | 1939 | M | 3 | 4 | 18 | 2 | .. | O. U. | + | 3 | 26 | 24 | ..... |
| 9 | 1940 | F | 23 | 28 | 28 | 3½ | .. | O. U. | + | 6 | 34 | 32½ | ..... |
| 10 | 1940 | F | 4 | 4 | 4 | .. | 10 | O. U. | + | 0 | 23½ | 28 | Propositus institutionalized because of mental retardation |
| 11 | 1940 | M | 34 | 34 | 37 | 4½ | .. | O. U. | + | 3 | 35 | 33 | ..... |
| 12 | 1940 | M | 12 | 12 | 12 | 4½ | .. | O. U. | + | 4 | 30 | 28½ | ..... |
| 13 | 1940 | M | 6 | 9 | 10 | .. | 10 | O. S. | + | 1 | 24 | 21 | ..... |
| 14 | 1940 | F | 3 | 3 | 3 | .. | 8½ | O. U. | + | 1 | 24 | 23½ | ?Propositus mentally retarded |
| 15 | 1941 | F | ? 3-6 | 21 | 38 | .. | 12 | O. D. | — | 0 | 27 | 25 | Diagnosis seems very probable, despite absence of pathological confirmation, since 4 pathologists agreed on it |
| 16 | 1941 | M | 7 | 10 | 10 | .. | 9 | O. S. | + | 1 | 26 | 23½ | Negro; evidences of considerable Caucasian admixture |
| 17 | 1941 | M | 22 | 28 | 29 | 3½ | .. | O. U. | + | 3 | 27½ | 27 | ..... |
| 18 | 1941 | F | 38 | 40 | 47 | 5 | .. | O. S. | — | 3 | 34 | 29½ | Manner of death suggests cerebral metastases, making diagnosis very probable, despite absence of pathological confirmation |
| 19 | 1941 | M | 59 | 59 | 59 | 8½ | .. | O. S. | + | 3 | 30½ | 24½ | ..... |
| 20 | 1941 | F | 2 | 2 | 2 | .. | 8 | O. U. | + | 2 | 42½ | 23½ | ..... |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | 1942 | M | 30 | 31 | 32 | .. | 10 | O. D. | + | .. | .. | .. | Patient an adopted child; no data available concerning parents and siblings |
| 22 | 1942 | M | 53 | 55 | 55 | 4½ | .. | O. S. | + | 3 | 40 | 37 | ..... |
| 23 | 1942 | F | 21 | 21 | 25 | .. | 9 | O. D. | + | 1 | 32½ | 30 | ..... |
| 24 | 1942 | M | 118 | 119 | 122 | .. | 16½ | O. D. | + | 4 | 37½ | 19½ | ..... |
| 25 | 1942 | M | 48 | 49 | 55 | 11½ | .. | O. U. | + | 2 | 30½ | 24 | ..... |
| 26 | 1943 | F | 4 | 6 | Refused | 1 | .. | O. U. | + | 0 | 23½ | 22½ | Patients identical twins; report by Falls [2] (cf. |
| 26 | 1943 | F | 6 | 11 | Refused | 1½ | .. | O. U. | − | 0 | 32½ | 22½ | our Fig. 1) |
| 27 | 1943 | M | 26 | 28 | 28 | .. | 9½ | O. U. | + | 4 | 44 | 40 | ..... |
| 28 | 1943 | F | 30 | 30 | 31 | .. | 9 | O. S. | + | 14 | 37½ | 37 | ..... |
| 29 | 1943 | M | ? 2 | 6 | 6 | 4 | .. | O. U. | + | 6 | 32 | 25½ | ..... |
| 30 | 1943 | M | 53 | 55 | 55 | .. | 10 | O. D. | + | 3 | 34 | 29½ | Patient mentally retarded |
| 31 | 1943 | F | 1 | 23 | 28 | .. | 8½ | O. S. | + | 2 | 22½ | 20½ | ..... |
| 32 | 1943 | M | 21 | 21 | 21 | .. | 8 | O. S. | − | 2 | 35½ | 34 | Pathological report cannot be located; diagnosis by 2 ophthalmologists |
| 33 | 1943 | F | 4 | 9 | 10 | .. | 7 | O. D. | + | 2 | 31½ | 29 | ..... |
| 34 | 1944 | M | 18 | 18 | 18 | .. | 7 | O. U. | + | 1 | 31½ | 31½ | ..... |
| 35 | 1944 | F | 50 | 51 | 52 | .. | 10 | O. S. | + | See "Comment" | See "Comment" | See "Comment" | Patient's mother had O. S. removed at age of 3½ yr. because of retinoblastoma; 4 of 8 maternal uncles and aunts thought to have retinoblastoma; no known ocular pathology in maternal grandparents; family reported by Falls [2] (cf. our Fig. 1) |
| 36 | 1944 | F | 6 | 7 | 11 | .. | 6 | O. D. | + | 1 | 30 | 23 | ..... |
| 37 | 1945 | M | 3 | 3 | 5 | 3½ | .. | O. U. | + | 0 | 29 | 28½ | ..... |
| 38 | 1945 | M | 3 | 3 | 3 | .. | 5 | O. D. | + | 2 | 24½ | 22½ | Patient grossly retarded mentally; internal hydrocephalus and maldevelopment of cerebral hemispheres |
| 39 | 1945 | M | 42 | 43 | 45 | .. | 8 | O. D. | + | 2 | 22½ | 20½ | ..... |
| 40 | 1945 | M | 15 | 20 | 36 | 3½ | .. | O. S. | + | 2 | 27½ | 27 | ..... |
| 41 | 1945 | F | 1 | 1 | 7 | .. | 5 | O. U. | + | 2 | 37½ | 33½ | ..... |
| 42 | 1945 | F | 20 | 20 | 27 | 4 | .. | O. S. | + | 2 | 29 | 23 | ..... |
| 43 | 1945 | F | .. | .. | .. | .. | .. | ..... | + | .. | .. | .. | Impossible to trace family |
| 44 | 1945 | F | 26 | 29 | 30 | .. | 6 | O. S. | + | 3 | 30 | 25½ | ..... |
| 45 | 1946 | F | 29 | 29 | 31 | .. | 5½ | O. S. | + | 1 | 22½ | 20½ | ..... |
| 46 | 1946 | F | 18 | 19 | 20 | .. | 4 | O. S. | + | 3 | 37½ | 32½ | ..... |
| 47 | 1946 | M | 1 | 27 | 27 | 3½ | .. | O. S. | + | 2 | 29½ | 24 | ..... |
| 48 | 1947 | M | 0 | 1 | 3 | .. | 2 | O. D. | + | 0 | 22 | 20 | ..... |
| 49 | 1947 | F | 5 | 5 | 38 | 3½ | .. | O. D. | + | 2 | 21 | 18½ | ..... |
| 50 | 1947 | F | 36 | 43 | 46 | .. | 6½ | O. S. | − | 2 | 30½ | 21 | ..... |
| 51 | 1947 | F | 4 | 4 | 4 | .. | 1½ | O. D. | + | 1 | 37½ | 36½ | ..... |
| 52 | 1947 | M | 20 | 23 | 27 | .. | 4½ | O. U. | + | 1 | 30 | 25½ | ..... |
| 53 | 1948 | M | 34 | 35 | See "Comment" | .. | 3½ | O. S. | − | 1 | 35½ | 35½ | Diagnosis confirmed by 3 ophthalmologists; child grossly retarded mentally and operation refused |

TABLE 1.—*Data on Seventy-Two Kindreds in Which One or More Cases of Retinoblastoma Have Occurred*—Continued

| Kindred No. | Year of Diagnosis | Sex of Patient | Age When Disease Was Noted by Parents, Mo. | Age When Patient Was First Seen by Physician, Mo. | Age at Definitive Treatment, Mo. | Age at Death (If Deceased), Yr. | Age When Last Examined (If Alive), Yr. | Affected Eye or Eyes | Pathological Confirmation of Diagnosis | No. of Normal Sibs (Living More than One Yr.) | Age of Father at Birth of Patient | Age of Mother at Birth of Patient | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 54 | 1948 | F | 9 | 34 | 37 | .. | 4½ | O. S. | See "Comment" | 2 | 35½ | 32 | Diagnosis by 5 ophthalmologists; eye removed only after extensive irradiation, and definite tumor cells not observed |
| 55 | 1948 | F | 4 | 7 | 7 | .. | 1½ | O. U. | + | 1 | 26½ | 27½ | ..... |
| 56 | 1948 | M | 2 | 2 | 2 | .. | 1 | O. D. | + | 1 | 26½ | 25 | ..... |
| 57 | 1948 | M | 15 | 15 | 15 | .. | 1½ | O. D. | + | 1 | 28 | 28 | ..... |
| 58 | 1948 | F | 30 | 31 | 35 | .. | 3 | O. U. | + | 1 | 53½ | 23 | Parents first cousins once removed |
| 59 | 1948 | F | 14 | 16 | 16 | .. | 2 | O. U. | + | 1 | 18 | 18½ | ..... |
| 60 | 1948 | F | 45 | 45 | 47 | .. | 5 | O. S. | + | 0 | 24 | 24½ | ..... |
| 61 | 1948 | M | 25 | 25 | 25 | .. | 2 | O. S. | + | 0 | 44 | 40 | ..... |
| 62 | 1948 | M | 8 | 8 | 9 | .. | 4 | O. S. | + | 0 | 25½ | 25½ | ..... |
| 63 | 1949 | M | 13 | 16 | 16 | .. | 1½ | O. S | + | 0 | See "Comment" | See "Comment" | Father had bilateral retinoblastoma, with enucleation at age of 1 yr.; paternal grandfather aged 29 and paternal grandmother aged 26 at birth of father (cf. Fig. 1) |
| 64 | 1949 | M | 21 | 23 | 24 | .. | 2 | O. U. | + | 2 | 32 | 32 | ..... |
| 65 | 1949 | F | 20 | 28 | 28 | 2½ | .. | O. D. | + | 4 | 39 | 37 | ..... |
| 66 | 1949 | M | 21 | 21 | 22 | .. | 3 | O. S. | + | 2 | 40 | 28½ | ..... |
| 67 | 1950 | M | 1 | 1 | ? | .. | ½ | O. U. | + | 0 | 27 | 20½ | Maternal first cousin once removed d. at age of 9 yr. of malignant glioma of right cerebral hemisphere |
| 68 | 1950 | M | 9 | 12 | 12 | .. | 1½ | O. U. | + | 1 | 36 | 29½ | ..... |
| 69 | 1950 | M | 3 | 3 | 7 | ½ | .. | O. U. | + | 1 | 28 | 25 | ..... |
| 70 | 1950 | F | 36 | 42 | 42 | .. | 4 | O. S. | + | 0 | 30 | 29 | ..... |
| 71 | 1950 | F | 22 | 23 | 23 | .. | 2 | O. U. | + | See "Comment" | See "Comment" | See "Comment" | Mother's right eye enucleated at age of 1½ yr. because of retinoblastoma; maternal aunt had both eyes removed at age of 3 yr. because of retinoblastoma (O. U.); maternal great aunt reported to have died at age of 1 yr., blind at death (cf. Fig. 1) |
| 72 | 1951 | M | 12 | 14 | 14 | 1 | .. | O. U. | + | See "Comment" | See "Comment" | See "Comment" | Father's right eye enucleated in Palermo, Sicily, at age of 1½ yr. because of tumor; paternal grandfather aged 41 and paternal grandmother aged 29 at father's birth; no other malignant neoplasm in family |

### THE INCIDENCE OF THE DISEASE

The average age at which this disease comes to medical attention is approximately 2 years. On the average, then, there is a two-year lag between birth and detection, for which reason, in calculating incidence, one will be more nearly accurate if one uses not births for 1938-1947 but births for 1936-1945, as shown in table 2. Under these conditions, the incidence of the disease is 52 in 1,054,985 births, or 0.0000493, with a 19 in 20 probability that the "true" figure lies between 0.0000368 and 0.0000647, as calculated by the method of Stevens.[5] (The affected identical twins in family 26 have been counted as a single case.) It should be emphasized that this is a minimum figure. It would be too much to expect, in a study of this type, that one had located all cases. On the other hand, from the manner in which information concerning any given case tended to come from several independent sources, it is unlikely that any substantial number of cases has gone unreported.

### THE MODE OF INHERITANCE

The family histories obtained are in conformity with the hypothesis concerning the mode of inheritance which was outlined in the introduction. Those kindreds in which more than one case of the disease was reported are shown in Figure 1. Kindreds *2*, *62*, and *72* can be interpreted in terms of the appearance of the dominant gene in one generation as a result of mutation, with the transmission of that gene to approximately half the children of the affected members in the next generation. Kindreds *4*, *35*, and *71*, on the other hand, suggest that the mutant gene failed to exert its usual effect in the person who first received it, but did manifest itself in this person's children. In kindred *71* we face the possibility, if the dubious case in the second generation is accepted, that the gene was transmitted through unaffected members for two generations. In kindred *35* the gene appears to have been transmitted through unaffected members two generations apart. These three pedigrees could also be interpreted in terms of recessive inheritance, but the ratio of affected to normal (13:10) offspring among the children of normal parents is against this hypothesis, as it is in similar "horizontal" constellations in the literature. Furthermore, in kindreds *35* and *71*, to account for the affected offspring from marriages of normal and affected persons, we should have to postulate in all three instances that the affected person married a carrier of the same recessive gene—a very unlikely event. In the 65 remaining isolated cases included in this series, and not pictured in Figure 1, the appearance of the disease may be interpreted as due to a dominant mutation—those members of this group who survive and reproduce will transmit

TABLE 2.—*Number of Sporadic Cases of Retinoblastoma Diagnosed per Year in the State of Michigan Between 1938 and 1947 as Compared with the Number of Births During a Similar Period.**

| Year | 1936 | 1937 | 1938 | 1939 | 1940 | 1941 | 1942 | 1943 | 1944 | 1945 | 1946 | 1947 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of births (place of occurrence) | 88,427 | 91,539 | 96,963 | 94,418 | 99,108 | 107,511 | 123,886 | 125,778 | 114,700 | 112,655 | .. | .. | 1,054,985 |
| Cases of retinoblastoma | .. | .. | 2 | 4 | 6 | 6 | 5 | 8 | 2 | 8 | 3 | 5 | 49 |

* Vital Statistics of the United States, 1945, Pts. 1 and 2, Natality and Mortality Data for the United States, Tabulated by Place of Residence, Bulletin 4329 and Bulletin 8732, National Office of Vital Statistics, Federal Security Agency, 1947.

5. Stevens, W. L.: Accuracy of Mutation Rates, J. Genetics **43**:301, 1942.

the gene (and the disease) to approximately half their children. Kindred *26* exhibiting the disease in identical twins, should, biologically speaking, be included with the sporadic cases. It cannot, of course, be definitely denied that in some of these isolated cases a recessive gene was operative. However, it is of some significance in this connection that only one of the marriages (58) is known to involve consanguinity—the proportion should be higher were recessive heredity involved in any substantial fraction of the cases.

A rough estimate of the number of persons who possess the gene but in whom retinoblastoma fails to develop (failure of penetrance) may be derived by excluding

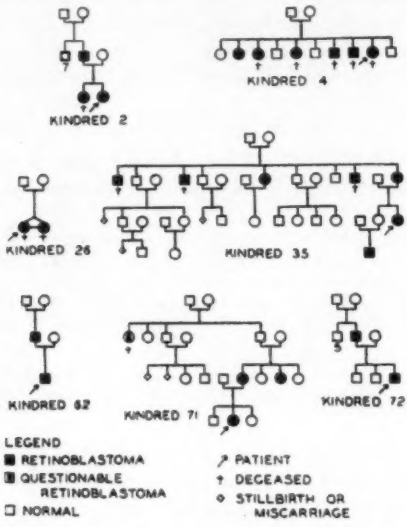


Fig. 1.—Chart showing the seven kindreds included in this study in which there occurred more than one case of retinoblastoma.

from consideration those cases in which there is an affected parent and, for the remainder, calculating the fraction

$$\frac{\text{Index cases with affected siblings}}{\text{Index cases with affected siblings} + \text{sporadic cases}} = \frac{1}{67} = 0.015$$

This is a minimum figure because of the possibility that in some of the apparently isolated cases (especially in the one-child families) the propositi will, with the passage of time, acquire affected siblings; but while it seems quite possible that in these data the fraction may be as great as 5%, it is unlikely that it is as great as 10%. This is a significantly lower estimate than that of Franceschetti and Bischler [10] (22%) but is in reasonable agreement with the estimate of Haldane [6] (10%).

It is quite possible that these "failures of penetrance" are more apparent than real. The histological anlage from which a retinoblastoma arises is unknown. Should it be in the nature of a small "cellular arrest," one or more collections of

6. Haldane, J. B. S.: Genetic Research in Britain, 1939-1945, Heredity **1**:3, 1947.

such cells could exist in an eye which to the ophthalmologist appeared completely normal. One could postulate that this lesion is always present but that in some few persons it fails to develop into a retinoblastoma, for reasons now obscure.

The parents of affected children are, of course, concerned over the probability of a recurrence in subsequent pregnancies. If the parent is likewise affected, then the probability would appear to be a simple 1 in 2, or, because of occasional failures of the gene to find expression, probably somewhat less. But when the parents are superficially normal, the question is more difficult to answer. On a strictly empirical basis, we may take all our index cases with normal parents and calculate the proportion of affected children among the siblings, which is $\frac{5}{126}$, or 0.039. This empirical figure is somewhat misleading when applied to the individual family. This is because the figure is based on two types of families, namely, those in which the disease occurs because the child has inherited a mutated gene originating at a late stage in gametogenesis, and in which the probability of a recurrence is essentially negative, and those in which the disease occurs because one of the parents, although clinically normal, is actually a carrier of the gene in question—in which case the probability of a recurrence is approximately 1 in 2. Unfortunately, we have at present no way of distinguishing between these two types of families. The empirical figure as here derived is probably an overestimate, since it so happens that the single sibship which contributes the numerator of the above-calculated fraction is composed of the children of a mentally subnormal woman, whose reproductive career was in no way tempered by the unfortunate fate of over half her children, whereas in many of the families contributing only a single child an abrupt termination of reproduction has followed the occurrence of the disease. A more nearly correct empirical figure would appear to be that derived above for failure of penetrance (0.015). Reese[7] has summarized the available data concerning the occurrence of retinoblastoma among the siblings of a child with this disease when both parents are normal. Most authors have failed to state the exact number of siblings involved, but in three series (including his own) in which this had been done the incidence was 1 in 378 siblings (0.0029). These figures likewise suggest that our empirically derived figure is an overestimate.

If two normal parents who have an affected child continue to reproduce and have a second affected child, it may be concluded that one of the parents carries a suppressed gene for retinoblastoma. In this case, the empirically derived figure of 0.039 no longer applies, and the probability of further affected children is approximately 1 in 2.

A special word should be said about the situation encountered in kindred *35*, which will be made clear by reference to Figure 1. Here, an affected woman had two daughters, one with the disease (the proposita) and one who on repeated ophthalmological examination seemed entirely normal. The affected woman was a member of a sibship of nine, four of whom, in addition to herself, certainly or very probably had retinoblastoma. It would appear that one of the parents of this sibship possessed an unexpressed retinoblastoma gene. It was obvious that the children of this woman's affected daughter had a 1 : 2 chance of manifesting the disease. However, it appeared that the normal daughter had escaped inheriting the gene, in which

7. Reese, A. B.: Heredity and Retinoblastoma, Arch. Ophth. **42**:119 (Aug.) 1949.

case her children should all be normal, and the parents were so advised. Yet the first child of the "normal" daughter, at the age of 7 mo., was found to have bilateral involvement, an even more tragic situation than that presented in the usual case of retinoblastoma, since a family in which the disease has once occurred can anticipate the unpleasant final details, with which the parents of a child with sporadic disease are, fortunately, unfamiliar. It would appear that the "normal" daughter had also received a retinoblastoma gene, but, for unknown reasons, the tumor had failed to develop. Even a single experience of this nature tends to make one very cautious in making a genetic prognosis for the children of the unaffected siblings of children with the disease.

### THE MUTATION RATE

If it is assumed that retinoblastoma always has a genetic basis and, further, that it depends upon the occurrence of mutation involving the same chromosomal locus, then the rate with which this mutation is appearing in the population of Michigan is expressed by the fraction:

$$\frac{\text{Frequency of sibships in which one or more affected children have been born to normal parents during a given period}}{\text{Total number of births in the population during the same period}}$$

In our data, the number of such sibships is 50, while the total number of births is 1,054,985. However, in one of these sibships (No. 4), in which six affected children were born to normal parents, the disease in all but one of these children was diagnosed outside the period of this study, so that statistically it would be better to omit this sibship from consideration. The proper fraction is therefore 49 in 1,054,985, or 0.0000464, with a 19 in 20 probability that the true value lies between 0.0000344 and 0.0000615. The mutation rate per gene, since each person possesses two representatives of all autosomal genes, is half this—0.0000232, or $2.3 \times 10^{-5}$, with a 19 in 20 probability that the true value lies between 1.7 and $3.1 \times 10^{-5}$.

It is possible that etiologically there are two types of retinoblastoma, one genetically determined and the other the result of factors the nature of which is not yet understood. It is also possible that the genetic variety of retinoblastoma may be due to the presence of any one of several mutations. Admittedly, there is at present no really satisfactory evidence that only one genetic locus is involved—in so assuming, one is guided by the principle of parsimony and the improbability that so specific a lesion would be determined by several different genes. Should only a portion of retinoblastoma be genetically determined, or should several genes be involved, the foregoing estimate of the mutation rate is, of course, too high. Evidence compatible with the hypothesis that in a portion of the cases of unilateral retinoblastoma the involvement is due to somatic, rather than germinal, mutation will be discussed later. Should the former be responsible, then another factor is contributing to an overestimate of the true mutation rate. On the other hand, inability to locate all the cases, as well as failure to correct the estimate for identical twin births and the death of infants from other causes prior to the age at which the tumor usually develops, would tend to result in an underestimate of the true rate.

As previously noted, Philip and Sorsby [3] have estimated that the mutation rate for the gene responsible for retinoblastoma is $1.4 \times 10^{-5}$. The basis for the difference between their value and ours lies in the fact that they utilized a figure for the frequency of the disease which is lower than ours. This frequency figure is derived from a paper by Griffith and Sorsby,[1c] in which it was postulated that the 59 cases

of retinoblastoma observed at the Royal Eye Hospital, London, in the 50 yr. between 1894 and 1943 represented all those occurring among the 1,934,764 births in London south of the Thames (the area served by this hospital) during this period. This led to an incidence of 1 in 32,793 births. Hemmes [8] estimated that in the Netherlands the disease occurs once in every 34,000 children. The general agreement between these two independent estimates is good; both appear to be significantly lower than our own. Whether this difference is real or reflects differences in the completeness of ascertainment is not clear. If real, then the interesting possibility emerges that the responsible gene may mutate with different rates in different populations.

## FACTORS INFLUENCING THE OCCURRENCE OF MUTATION

The present section is devoted to the analysis of a problem which has broad and far-reaching implications. Mutation tends to result in characters disadvantageous to the organism. This is because mutation apparently entails random change in the composition of the hereditary material, and such random change in any of the myriad finely adjusted forms of life can scarcely be for the better. Nature, in her geological

TABLE 3.—*Comparison of Month of Conception for Forty-Eight Cases of Isolated Retinoblastoma* Occurring Between 1938 and 1947 and Month of Conception for All Live Births in the State of Michigan During the Same Period*

| Month | Jan. | Feb. | March | April | May | June | July | Aug. | Sept. | Oct. | Nov. | Dec. | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of live-born infants conceived during that month.. | 88,363 | 83,185 | 84,985 | 87,547 | 82,065 | 90,111 | 84,126 | 87,443 | 88,682 | 94,354 | 93,409 | 90,715 | 1,054,985 |
| | 171,548 | | 172,532 | | 172,176 | | 171,569 | | 183,036 | | 184,124 | | |
| No. of children with retinoblastoma conceived during that month ..... | 6 | 4 | 6 | 4 | 5 | 5 | 3 | 0 | 4 | 3 | 5 | 3 | 48 |
| | 10 | | 10 | | 10 | | 3 | | 7 | | 8 | | |

* One sporadic case is omitted because the date of birth is unknown.

time, can afford to be profligate—if only one among a thousand mutations confers an advantage upon its possessor, this one can be saved and the others discarded. For any species there is an optimum mutation rate—too rapid an appearance of new forms could "swamp" the selective process; too slow an appearance would provide an insufficient material for the operation of natural selection, and the species would lose the ability to adapt genetically to a slowly, but constantly, changing environment. As viewed by the geneticist, then, each species represents a temporary equilibrium point between mutation and natural selection, an equilibrium point which persists because it is beautifully adapted to some ecological niche.

Any factor which tends to alter either the rate of occurrence of mutation or the pressure of natural selection may, over a long period of time, have far-reaching consequences for the organism involved. It has already been demonstrated that in a wide variety of plant and animal species the rate of mutation may be altered by extremes of temperature, irradiation, and certain chemical procedures, and that, further, some strains of a species have higher mutation rates than others. In the present section, we propose to analyze our material for clues to factors affecting the mutation rate. In the succeeding section, we propose to discuss the complement to this question, namely, the long-range effect of changing levels of ophthalmological care (i. e., altered selective values) with respect to this disease.

8. Hemmes, G. D.: Untersuchung nach dem Vorkommen von Glioma retinae bei Verwandten von mit dieser Krankheit behafteten, Klin. Monatsbl. Augenh. **86**:331, 1931.

1. *Secular Trends.*—From Table 2 it is possible to calculate whether the distribution of sporadic cases is at random within the 10-yr. period under consideration or whether there are significantly more cases in some years than in others. A $\chi^2$ test for the homogeneity of the distribution, the data being treated as a $2 \times 10$ table, yields a value of 8.31, with nine degrees of freedom. The probability of such a value on the basis of chance alone exceeds 50%; i. e., the chances are better than

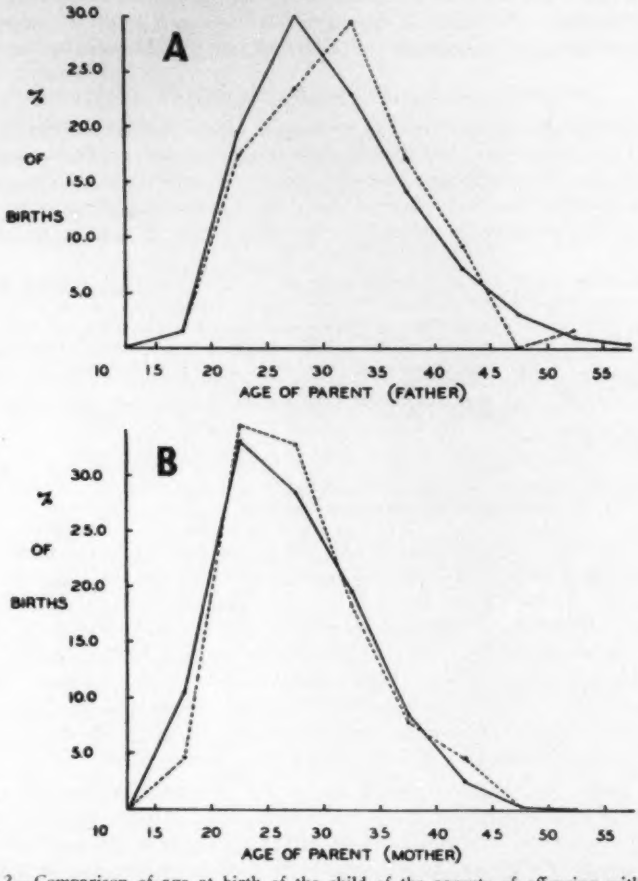


Fig. 2.—Comparison of age at birth of the child of the parents of offspring with isolated cases of retinoblastoma included in this study (broken line) and the parents of all children born in the State of Michigan between 1936 and 1945 (solid line). *A* represents correlation for fathers, and *B*, that for mothers.

even that there is no significant secular trend in the incidence of retinoblastoma during the period under study.

2. *Season of Conception.*—Table 3 presents a comparison of the month of conception in 48 isolated cases of retinoblastoma occurring between 1938 and 1947 with the month of conception for all live births occurring in the State of Michigan

during the same period, an approximation to the month of conception being derived by subtracting nine months from the month of birth. One isolated case has been omitted from the calculation because the date of birth is unknown. A $\chi^2$ comparison of the two distributions yields a value of 4.99, which, with five degrees of freedom, should be exceeded on the basis of chance alone approximately 4 times in 10.

3. *Effect of Parental Age.*—Figure 2*A* is a graphic comparison, expressed in per cents, of the age of all fathers at birth of the child in the State of Michigan between 1936 and 1945 with the age of the fathers of our retinoblastoma children. Figure 2*B* is a similar curve for the mothers. Table 4 presents the data on which these curves are based. A $\chi^2$ test of the identity of the two distributions, combining, because of paucity of cases of retinoblastoma, the two lowest and the four highest age groups, fails to reveal any grounds for the assumption that the two age curves are dissimilar (fathers: $\chi^2 = 2.714$, df $= 5$, $0.70 < P < 0.80$; mothers: $\chi^2 = 3.475$, df $= 5$, $0.50 < P < 0.70$).

The genetic situation presented by achondroplasia appears in many ways comparable to that encountered with retinoblastoma (Mørch [9]). The condition is postu-

TABLE 4.—*Comparison of Age of All Parents at Birth of Child in the State of Michigan Between 1936 and 1945 and Age of the Sixty-Four Parents of Children Manifesting Isolated Retinoblastoma Included in this Study* *

| Age Group,* Yr. | 10-14 | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50-54 | 55- | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| All fathers | 6 | 15,764 | 208,026 | 311,840 | 240,592 | 148,067 | 75,073 | 30,506 | 9,778 | 4,101 | 1,038,748 |
| Fathers of children manifesting retinoblastoma | .. | 1 | 11 | 15 | 19 | 11 | 6 | .. | 1 | .. | 64 |
| All mothers | 605 | 107,772 | 347,083 | 299,692 | 179,924 | 89,844 | 26,128 | 2,120 | 49 | 7 | 1,053,174 |
| Mothers of children manifesting retinoblastoma | .. | 3 | 22 | 21 | 10 | 5 | 3 | .. | .. | .. | 64 |

* Inequalities in the totals of mothers and fathers is due to frequent omission of age of parent from birth certificates.

lated to be due to a dominant gene, with sporadic cases the result of mutation. In his analysis of factors which might affect the mutation rate, Mørch found only one of possible significance. It appeared that the mutation rate was higher in older parents. While our own data fail to confirm this finding in a statistically significant fashion, it nevertheless is noteworthy that the trend is in the same direction as that observed by Mørch.

It is customary in studies of this type to test for the effect of parity, as well as of age. However, it is not felt that the present material lends itself to such an analysis. This is because too many of the kindreds under discussion are still incomplete and, further, because in a significant number of families there has been voluntary limitation of sibship size after the diagnosis of retinoblastoma, either for economic reasons, because of the added financial burden which the disease imposes upon the families involved, or because of medical advice to the parents to refrain from further childbearing. These sources of bias are thought to be so significant as to invalidate any analysis along these lines.

4. *Relation to Urban Versus "Rural" Life.*—Figure 3 is a graphic representation of the distribution in the State of Michigan at the time this study was conducted of the families with retinoblastoma diagnosed between 1938 and 1947. Analysis of

9. Mørch, T.: Chondrodystrophic Dwarfs in Denmark, with Special Reference to Inheritance of Chondrodystrophy, Copenhagen, Ejnar Munksgaard Forlag, 1941, p. 200.

the question whether there is any tendency for this mutation to be associated with urban as against rural life is complicated by the absence of a hard-and-fast distinction between urban and rural existence. A first approximation to the answer is, however, possible. Arbitrarily, we will assume that persons dwelling in cities with a population greater than 25,000 are subject to "urban" conditions, while those living in population centers smaller than this or removed entirely from population centers are subject to "rural" life. In 1940 there were 18 cities in this state with more than 25,000 inhabitants, their populations ranging from 25,087 to 1,623,452. These centers contained a total of 2,692,831 inhabitants, whereas in the rest of the state there were 2,563,275 inhabitants. Of the 99,021 births to residents of the State of Michigan in 1940, 49,809 were to persons residing in cities of 25,000 or more inhabitants, whereas 49,212 were to persons living either under strictly rural con-

Fig. 3.—Distribution of the cases of retinoblastoma diagnosed in the State of Michigan between 1938 and 1947. Each dot represents a case. Eleven in the southeast corner of the state represents the number of cases in the cities of Detroit and Royal Oak.

ditions or in towns of less than 25,000 inhabitants, the percentage ratio of the two being 50.3 : 49.7. However, of 48 isolated patients with retinoblastoma observed between 1938 and 1947 the parents of 18 were residing at the time of this investigation in one of these 18 cities, while the parents of 30 were living outside these cities, a ratio of 37.5 : 62.5. (One isolated case is not included because the child had been adopted and no information was available concerning the parents.) Assuming that place of residence is highly correlated with place of birth, and assuming that the figures for 1940 are more or less typical of the period under study, the expected distribution of urban and rural cases would be 24.1 and 23.9, respectively. The $\chi^2$ value for the difference between observed and expected distribution, as calculated from a $2 \times 2$ table, is 1.550, which, with one degree of freedom, has a $P$ value lying between 20 and 30%. The present data, then, are insufficient to establish a statistically significant urban-rural differential.

In passing, it may be pointed out that many factors can be envisioned which may have biased these figures in one direction or the other, such as urban-rural differences in the level of medical practice, failure of Detroit ophthalmologists and hospitals to report their cases to the same extent as do ophthalmologists and hospitals in the smaller communities, and a tendency for the parents of affected children to move about more than usual. On the basis of the present data it is not possible to hazard an opinion as to the relative importance of any of these factors.

It is perhaps noteworthy that three of our cases occurred in one small town on the St. Clair river, with a population of 3,471. While no significance can be attached to the finding, the odds against such an occurrence are high.

The difference between Philip and Sorsby's [3] estimate of the mutation rate and ours has already been discussed. The population from which their frequency figure was derived appears to have been strictly urban. If really present, an urban-rural difference with respect to the frequency of the disease would be a possible contributing factor to the discrepancy in our respective findings.

5. *Race.*—Of the over 1,000,000 births occurring in the state between 1936 and 1945, 4.21% were to Negro parents. However, only one of our 72 cases of retinoblastoma (1.39%) involved Negro parents. Although the father of this child was not seen, the appearance of the patient, her sister, and her mother suggested a strong Caucasian admixture. The hypothesis that the mutation occurs less frequently in Negroes than in Caucasians may be considered. Inasmuch as the great majority of Negroes residing in this state are to be found in Detroit and other cities, a lower rate among Negroes could be a factor in the possible urban-rural differential discussed in the preceding section.

6. *Physical and Mental Characteristics of Families in Which Retinoblastoma Has Occurred.*—Nothing is known concerning the factors regulating the distribution of mutations in human populations. By analogy with the results of investigations of the fruit fly Drosophila, it seems possible that some persons, or groups of related persons, exhibit higher mutation rates than others. Since at least one mutation, and possibly more, has occurred in one or the other parent in our cases of sporadic retinoblastoma, or, in those instances in which there are several cases in a family, in a more remote ancestor, it is of some interest to consider the characteristics of the families under consideration.

(*a*) Children with Retinoblastoma: Of the 53 children with retinoblastoma occurring between 1938 and 1947, 33 were living at the time of the study; 19 were dead, and the status of one was unknown. All but four of the 33 living children were seen by us. Except for the retinoblastoma, the medical histories of these children were not unusual. There were no characteristic physical findings. Nevi, hemangioma, and café-au-lait spots were not thought to be especially frequent among these children. However, three of them were definitely mentally retarded, one revealing evidence of a profound defect of the central nervous system. In addition, a fourth child was probably mentally retarded, but it was thought that the psychometric information available was insufficient for a decision. Of the 19 deceased children, one was also known to have been mentally retarded. The records on several of the remaining children are unsatisfactory with respect to the mental status. Many of the 20 patients to come to our attention since 1948 are too young for decision concerning any but a major mental defect, but of the 18 living children, one is

known to exhibit manifestations of severe mental defect. It seems possible that retinoblastoma will be found to be associated with mental defect significantly oftener than can be explained on the basis of chance alone. Inasmuch as only one of these children received radiation to the orbit prior to the recognition of the retardation, the irradiation can scarcely be assigned a role in the mental defect. One may perhaps be permitted to speculate on the possibility that the mental retardation reflects a tendency to an aberration of elements of the central nervous system, an aberration which is most apparent in the retina.

(*b*) Siblings of Children with Retinoblastoma: In addition to the pregnancy which terminated in the birth of the child in whom retinoblastoma developed, the mothers of our subjects had 176 other pregnancies, of which 24 (13.6%) terminated in miscarriages, 2 (1.1%) in stillbirths, and 150 (85.3%) in live births. On the basis of our own experience, as well as the data in the literature, this would appear to be in keeping with the usual findings regarding types of termination of pregnancy. Sixteen of the 150 live-born children were dead, five because of retinoblastoma, and the rest for a variety of reasons. On the basis of the information collected in the course of this investigation, the 134 living siblings presented no particular characteristics which would distinguish them from any randomly assembled group of children and young adults of comparable size. Only one presented clear-cut genetic disease—a girl with epidermolysis bullosa.

Two siblings were known to be mentally deficient, one of these (now dead) having mongolism. This incidence is in contrast to the incidence of mental defect in retinoblastoma, discussed above. However, it should be pointed out that our information concerning the occurrence of mental defect is somewhat less reliable for siblings than for patients.

(*c*) Parents of Children with Retinoblastoma: In the course of this study, we have met and talked with, and in approximately half the cases carried out physical examinations on, 94 nonaffected parents of children with retinoblastoma. The danger of "general impressions" in clinical medicine is well recognized. With this danger clearly in mind, we, nevertheless, venture the opinion that the persons in question do not differ strikingly from a randomly assembled group of similar age and with a comparable social background. This, of course, does not exclude the possibility that a detailed clinical study might bring out minor, but significant, differences from the "norm."

7. *Ophthalmological Findings in the Families in Which Retinoblastoma Has Occurred.*—Attention has already been drawn to the fact that in a certain proportion of persons who receive the gene responsible for retinoblastoma the tumor apparently fails to develop. The possibility exists that in some or all of these apparent exceptions a retinoblastoma actually does develop at some stage in the person's existence, but that, for reasons unknown, it undergoes spontaneous regression. In an attempt to obtain data on this point, ophthalmological examinations were performed on 94 apparently normal parents of children with retinoblastoma and on 97 siblings of such children, as well as on 28 children with unilateral retinoblastoma. Particular attention was devoted to a search for retinal scarring. The findings may briefly be summarized as follows:

(*a*) Position of the Eyes in the Primary Position: Five parents (5.3%) presented an alternating divergent strabismus. No manifest strabismus was demon-

strable in the siblings. For obvious reasons, this observation could not be made on the affected patients.

(*b*) Latent Muscle Imbalance: Four parents (4.3%) exhibited esophoria, the rest showing some degree of exophoria. Eight siblings (8.3%) were found to be esophoric, the rest having exophoria of varying degrees.

(*b'*) Color of Iris: The patients, their parents, and their siblings did not differ significantly in the proportions exhibiting blue, hazel, and brown eyes. The frequently reported observation that iris freckles are commonly associated with malignant melanoma of the choroid led us to search carefully for the presence of such freckles in this group. That there is no specific relationship between iris freckles and retinoblastoma is suggested by the absence of such freckles in the affected patients and the rather low (normal) incidence in their siblings (3.1%) and parents (8.5%). That there may be some association between iris freckles and advancing age is suggested by the higher incidence of the freckles in parents than in their children.

(*c*) Lens: Four of the patients (14.3%) presented lenticular abnormalities in the remaining eye, three exhibiting the anterior axial embryonic cataract of Vogt and one showing congenital pigmentary deposits in the anterior capsule. Anterior axial cataract was seen in three (3.1%) of the siblings and in seven (7.4%) of the parents. In addition, one parent exhibited a cuneiform cataract, and one, a minute subcapsular cataract. The fact that the observed incidence of anterior axial cataract in this series is so much lower than the incidence of 20 to 30% usually accepted as normal may be attributed to our inability to perform slit-lamp examinations in the homes.

(*d*) Optic Nerve Head: One patient exhibited high central branching of the retinal artery; one, congenital gliosis, and one, a congenital crescent of the disk border. One mentally deficient patient was found to have secondary optic nerve atrophy associated with nystagmus. Among the siblings, there was high central branching in 10 (10.3%), while 2 had congenital gliosis and 1 a congenital crescent. Mild to moderate situs inversus vasorum was seen in six siblings (6.2%). Among the parents, six (6.4%) had high central vascular branching; four (4.3%), congenital gliosis, and three (3.2%), a congenital crescent. One person was observed to have medullated nerve fibers.

(*e*) Retina: Among the patients, three (10.7%) were found to have old, isolated, peripheral chorioretinitis, the areas varying in size from ⅛ to 1 disk diameter. One of these lesions was sufficiently gliotic in appearance to suggest retinoblastoma. However, it has not varied in appearance during the four years that it has been under observation. None of the siblings was found to have chorioretinitis, although seven (7.2%) exhibited an extensive lack of retinal pigmentation and one each showed lamina vitrea verrucae of the lamina vitrea (basalis), congenitally tortuous retinal vessels, and stippled pigmentation of the macula. Among the parents, six (6.4%) exhibited chorioretinitis, no areas being more extensive than 1 disk diameter, but no specific signs of retinoblastoma (calcification, extensive gliosis) were seen. Myopic degeneration was seen in one person; verrucae of the lamina vitrea, in three, stippled pigmentation of the macular area, in one, and extensive lack of retinal pigmentation, in one. Neither of the parents of kindred 4

(Fig. 1), one of whom certainly carried an unexpressed gene for retinoblastoma, exhibited significant retinal defects.

(*f*) Visual Acuity: No more defects were observed than one might normally expect.

It is thought that all the above findings are such as might be encountered in any randomly assembled group comparable with regard to age, sex, occupation, etc. No findings suggestive of the occurrence and spontaneous regression of a retinoblastoma were encountered.

8. *Incidence of Malignant Neoplasms in Families with Retinoblastoma.*—An attempt has been made to determine whether there is an increased incidence of malignant neoplasms among the relatives of children who show retinoblastoma, i. e., whether the appearance of this tumor is related to a "cancer diathesis" on the part of the affected families. The siblings, parents, and uncles and aunts of affected children are so far below the usual age of onset of malignant disease that an analysis

TABLE 5.—*Occurrence of Malignant Neoplasms Among the Grandparents of Seventy-Two Children with Retinoblastoma, with Control Figures* *

| Retinoblastoma | | Controls | |
|---|---|---|---|
| Grandparent alive | | Grandparent alive | |
| No malignant disease | 175 | No malignant disease | 206 |
| Definite malignant disease | 3 | Definite malignant disease | 1 |
| History suggestive of malignant disease | 2 | History suggestive of malignant disease | 0 |
| | 180 | | 207 |
| Grandparent deceased | | Grandparent deceased | |
| No malignant disease | 72 | No malignant disease | 61 |
| Definite malignant disease | 8 | Definite malignant disease | 11 |
| History suggestive of malignant disease | 6 | History suggestive of malignant disease | 2 |
| | 86 | | 74 |
| Data inadequate | 22 | Data inadequate | 15 |
| | 288 | | 296 |

* For further explanation, see text.

of the occurrence of malignant neoplasm in these groups would probably not contribute greatly to the problem. The grandparents, however, are well within the critical age groups. The difficulties of establishing by the anamnestic approach either cancer-prevalence figures or over-all mortality rates for cancer are well known. Ignorance on the part of the informant, inadequate diagnostic studies, and inability to obtain verifying information from physicians and hospitals all combine to make the data, at best, approximate. A particular effort has been made to verify as many diagnoses as possible. The available data concerning the 288 grandparents of our 72 propositi are summarized in Table 5. Of the 86 grandparents now deceased on whom there is some information, eight (9.3%) certainly died of cancer, and for six more (7.0%) there is a strong possibility of cancer but confirmation is lacking. Assuming that half of these seven actually died of neoplastic disease, the total incidence may be placed at 12.8%. Of 180 grandparents still living on whom there are definite data, three (1.7%) have a verified diagnosis of cancer, with two more (1.1%) suspect.

An attempt has been made to evaluate the significance of these findings by several approaches. One method entails a comparison of the findings in this group with those in a control group composed of the grandparents of 74 children between the

ages of 1 mo. and 11 yr. seen at the Heredity Clinic during the past several years, the only basis of selection being that information was available on the present health or cause of death of at least three of the four grandparents. This involved a selection of families on whom the available data were relatively complete. The findings are summarized in Table 5. A comparison by the $\chi^2$ method of the frequency of death certainly or probably due to malignant disease in the two groups reveals no significant difference, the controls exhibiting, if anything, a higher frequency. The groups involved are admittedly small, and slight differences might well be obscured by chance variations.

A second method of evaluating the significance of our findings consists in comparing these data with certain vital statistics which Dr. Harold F. Dorn, of the National Cancer Institute, has made available. The grandparents of our propositi may be assumed to be drawn from a population all of whose members have reached the age of 30. The mortality from cancer among the deceased grandparents may, accordingly, be compared with the expected mortality from cancer in a group of persons all of whom have reached the age of 30. To be accurate, this comparison should be performed only when all the grandparents have died, since the fraction dying early might not be representative of the group as a whole. The present comparison must, therefore, be regarded as a first approximation. According to Dr. Dorn, on the basis of the 1900-1902 mortality statistics, the chances per 1,000 of eventually dying of cancer at the age of 30 were 54 for men and 81 for women. On the basis of the 1939-1941 statistics the chances were 118 for men and 145 for women, or an over-all average for both sexes of 100. This is in satisfactory agreement with the figure of 9.3 to 12.8% observed in our grandparental group. Of 180 living grandparents, the age is known for 177. From figures on the prevalence rates of cancer per 100,000 population per year supplied by Dr. Dorn, based upon preliminary unpublished data for morbidity surveys conducted by the National Cancer Institute, it can be calculated that in a group of 177 persons with the age composition of the living grandparents included in this study, the expected number of diagnoses of cancer is 3.12, a figure with which our own findings agree satisfactorily.

### FIVE-YEAR SURVIVAL VALUES AND POSSIBLE FUTURE TRENDS IN PREVALENCE OF THE DISEASE

In the foregoing section, it has not proved possible to identify any factor capable of exerting a significant effect on the mutation rate. In the present section, we shall assume that the mutation rate will remain relatively constant in the years to come and shall inquire into the possible effect of changing levels of medical care on the prevalence of retinoblastoma. It may be assumed that 100 years ago the gene was eliminated either in the same generation or (because of nonpenetrance) at most one or two generations after it arose. The situation today is potentially quite different. Table 1 reveals that in our own data, of 37 children who had been followed at least five years when last seen, 23 (62.2%) were still alive. Other investigators of the past several decades have recorded similar, or even higher, survival rates in a randomly assembled series of patients: Davenport,[10] 70.4% of 27 patients; Pap-

10. Davenport, R. G.: Report on the Cases of Glioma Retinae Treated at the Royal London Ophthalmic Hospital During the Years 1915-1924, Brit. J. Ophth. **10**:474, 1926.

olczy,[11] 60% of 20 patients; Tüshaus,[12] 90% of 10 patients; Parkhill and Benedict,[13] 35% of 31 patients; Tice and Curran,[14] 50% of 12 patients, and Philip and Sorsby,[3] 86.8% of 53 patients. Reese, Merriam, and Martin [15] have reported five-year survivals in 63.2% of a series of 19 patients with the more unfavorable bilateral disease.

From an analysis of the results of Table 1, it can be determined that for the 67 cases for which such data are available the mean age when the parents first suspected an abnormality of the child's eye was 19.9 mo., the mean age at which a physician was first consulted was 22.7 mo., and the mean age at which definitive treatment was initiated was 25.4 mo. Standard errors have not been calculated because of the manner in which the distribution is skewed to the right. The delay in consulting a physician will probably diminish as the "medical awareness" of the public continues to rise. The delay between the time a physician was consulted and definitive therapy initiated was compounded of many elements, such as failure of the physician to make the diagnosis, desire of the physician making the diagnosis to have confirmation, "shopping around" on the part of the parents, and inability of the parents to accept the recommendation of enucleation. These sources of delay will probably also diminish with the passage of time. It may be assumed that during the centuries to come as many as 70% of the children in whom the disease develops will routinely be saved.

The percentage of cases of bilateral retinoblastoma in the literature ranges from 8.5 to 21.7.[16c] This figure is probably lower than the true proportion of cases of bilateral involvement, since in an appreciable fraction of cases reported when the tumor is unilateral the disease may ultimately become bilateral. Figures concerning the proportion of five-year survivors whose disease is bilateral in randomly assembled series are not extensive—in three series it was found to be 20.6%.[16] Of the 23 five-year survivors in our own series, 21.7% had bilateral disease. However, Griffith and Sorsby [16c] and Franceschetti and Bischler [16c] have drawn attention to an apparent tendency of the incidence of bilateral disease to be higher in "vertical" and "horizontal" constellations than in isolated cases, being in the neighborhood of 60%. The same tendency is apparent in our data, where in the six families in which there are multiple cases (excluding the identical twins) the disease is definitely bilateral in 11 of 24 cases (45.8%); information is unsatisfactory regarding a 12th case. Even allowing for the fact previously pointed out above, namely, that the reported frequency of cases of bilateral retinoblastoma was probably lower than the true frequency, there appears to be more bilateral disease when several cases occur in a family than when the case is sporadic. No satisfactory explanation for this has been advanced. A possibility which would seem to deserve consideration is that the gene in question mutates in somatic as well as germinal tissue. A somatic mutation, which might or might not involve the gonads, and so be liable to trans-

11. Papolczy, F.: Zur Prognose des Glioma retinae, Klin. Monatsbl. Augenh. **99**:355, 1937.

12. Tüshaus, R.: Zur Prognose des Glioma retinae und des Uvealsarkoms, Klin. Monatsbl. Augenh. **105**:41, 1940.

13. Parkhill, E. M., and Benedict, W. L.: Gliomas of Retina: Histopathologic Study, Am. J. Ophth. **24**:1354, 1941.

14. Tice, G. M., and Curran, E. J.: Treatment of Retinoblastoma: Radiation Therapy Supplementing Surgical Treatment, Radiology **42**:20, 1944.

15. Reese, A. B.; Merriam, G., and Martin, H. E.: Treatment of Bilateral Retinoblastoma by Irradiation and Surgery, Am. J. Ophth. **32**:175, 1949.

16. Davenport.[10] Tüshaus.[12] Tice and Curran.[14]

mission to the next generation, might be expected to involve only one eye in a certain proportion of cases. For the purposes of this calculation, we shall adopt a figure of 50% of bilateral disease in cases involving "direct" transmission.

Persons who are amaurotic in consequence of bilateral retinoblastoma undoubtedly show a greatly reduced marriage rate, and those who do marry, like the blind in general, will have few children. One may tentatively set the effective fertility of this group at or near zero. Persons who have lost only one eye are, on the other hand, not greatly handicapped—let us place their effective fertility at or near normal. In the absence of specific measures to discourage reproduction on the part of persons afflicted with retinoblastoma, then, the net effective fertility in all cases involving germinal mutation will approximate $0.7 \times 0.5 \times 1.0$, or 0.35. In other words, in the absence of any restriction on propagation, with the present levels of medical care, approximately 35% of the genes for retinoblastoma arising in one generation through mutation will be carried over to the next generation. If in that generation, however, the survival rate for persons with the disease is again 70%, the proportion of patients with bilateral disease (nonfertile persons) among the descendants of this 35% is again 50%, and if the patients with unilateral retinoblastoma have a near-normal fertility, as postulated above, the contribution of this 35% to the succeeding generation will be only $0.35 \times 0.7 \times 0.5 \times 1.0 \times m$, where $m$ is the mutation rate, or $0.1225\ m$. The general expression for the frequency of retinoblastoma at any given number of generations from an initial point of departure will therefore be

$$f = m + m\,lbr + ml^2b^2r^2 + ml^3b^3r^3 + \ldots ml^xb^xr^x$$

or

$$f = m(1 + lbr + l^2b^2r^2 + l^3b^3r^3 + \ldots l^xb^xr^x)$$

where $f$ is the frequency of retinoblastoma at the $x$th generation; $m$, the mutation rate for the gene (0.0000232); $l$, the mortality from the gene (0.7); $b$, proportion of patients with unilateral retinoblastoma (0.5); $r$, fertility of patients with unilateral disease (1.0), and $x$, number of generations that have elapsed.

We may, if we wish, write this in another form by designating the net selective disadvantage as $s$, equal to $(1\text{-}lbr)$, in which case the equation becomes

$$f = m\,[1 + (1\text{-}s) + (1\text{-}s)^2 + (1\text{-}s)^3 + \ldots (1\text{-}s)^x]$$

At $x = \infty$,

$$[1 + (1\text{-}s) + (1\text{-}s)^2 + (1\text{-}s)^3 + \ldots (1\text{-}s)^x] = \frac{1}{s}$$

and the equation becomes an expression well known to the population geneticist, $f = \frac{m}{s}$. In the derivation of this expression, the possibility of back mutation has been ignored; this would ordinarily be a negligible factor. Thus, with the present levels of medical care and unrestricted propagation, the frequency of the gene will increase, at first rapidly, then more slowly, until it reaches an equilibrium point. At this new equilibrium point, to which there will be a satisfactory approximation in eight generations, the gene will be 1.538 times as frequent as originally.

The approximate nature of this calculation cannot be too strongly emphasized. Nevertheless, it is sufficiently accurate to serve to give focus to the problem. While with the improved medical care of the past century there will be an appreciable

increase in the frequency of retinoblastoma, it will not, on the other hand, become a major ophthalmological problem in the foreseeable future. In this connection, however, it is important to point out that this disease is only one of a number of inherited pathological conditions where natural selection has recently been relaxed. In time it should be possible to synthesize a balanced picture of the frequency trend with respect to a considerable number of these diseases.

Two possible extreme developments of the future should be considered at this point. Were none of the persons with retinoblastoma to propagate, then the frequency of the gene would stabilize at $m$, the mutation rate. Should, on the other hand, medical science succeed in saving essentially all patients with this disease, and should the reproduction of persons with both unilateral and bilateral retinoblastoma reach normal, in consequence of unforeseeable social trends, the frequency of the disease would increase sharply, so that eight generations after such a trend was initiated the frequency of the gene would be approximately $8\ m$; roughly, 1 in each 2,700 persons would show the condition.

## SUMMARY AND CONCLUSIONS

An attempt has been made to establish a complete roster of cases of retinoblastoma occurring in the State of Michigan between 1938 and 1947 and to study in some detail the families in which these cases occurred. Fifty-three cases occurring in 52 families have been located. Pathological confirmation of the diagnosis was available for 48 cases. An additional 20 cases occurring in as many families during the period 1948 to 1951 have also been studied; no attempt has been made to establish a complete roster for these years.

The incidence of the disease is calculated to be approximately 1 for each 20,288 live births.

The family histories obtained in the present material are consistent with the hypothesis advanced by several other investigators, that the development of a retinoblastoma depends upon a single dominant gene, which does not always find expression.

Because of the fatal nature of retinoblastoma, the gene responsible for the condition is under strong negative selection pressure. That the condition persists at all is due to the appearance in each generation, as a result of mutation, of new genes determining the development of the disease. The rate of mutation ($m$) to this gene is calculated to be $2.3 \times 10^{-5}$ per generation.

The data have been analyzed for the existence of factors capable of influencing the mutation rate. No secular trend is apparent. The season of conception appears to have no effect. It could not be shown that parental age was a factor. Although there was a slightly higher rural than urban frequency, the difference was not statistically significant. No increased mortality due to malignant neoplasms was noted in the grandparents of our patients, although the data are, of course, limited.

Children with retinoblastoma may be mentally defective oftener than one would expect on the basis of the known incidence of mental defect—at least $5 + 1$ (?) in the series of 73. No other significant association of retinoblastoma with ocular, physical, or mental characteristics was noted. The parents and siblings of children with retinoblastoma were not thought to differ in any very apparent fashion, ophthalmologically or otherwise, from a cross section of the normal population.

The outlook for this disease has changed greatly in the past half-century. It is estimated that at present the five-year survival rate is close to 70%. Among five-year survivors who inherit the disease from a parent, approximately 50% will have bilateral disease.

If it is accepted that the patients with bilateral disease seldom reproduce, whereas the survivors with unilateral disease have a reproductive rate of about normal, then a first attempt at calculating the future frequency of the disease can be undertaken. Using a formula derived in the text, it can be shown that the frequency under these conditions should increase until at the end of eight generations a near-maximum frequency of 1.54 times the present frequency is reached.

It is pointed out that if persons with the disease never reproduced, the frequency of the gene would stablize at $m$. If, on the other hand, a 100% effective treatment were developed, and if survivors reproduced at a normal rate, the frequency of the gene would increase by $m$ each generation, so that in eight generations, the disease would have eight times its present frequency.

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# ORBITAL PSEUDOTUMORS

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PSEUDOTUMORS of the orbit are tumors in the strict sense of the word but not in the sense of "neoplasm," the prefix "pseudo" being used to differentiate them from true neoplasms of the orbit. Ophthalmic pathologists should use the word "pseudotumor" only in this general sense and should qualify the diagnosis further by reporting pseudotumor inflammatory, pseudotumor granulomatous, pseudotumor cystic, pseudotumor cholesteatomatous, etc. If such a classification were adopted generally, much of the confusion concerning this term would be eliminated. In this paper, I shall use the term "pseudotumor" to refer to any tumor of the orbit which is not a true neoplasm, such as a carcinoma or cylindroma.

## INCIDENCE

Pseudotumors of the orbit, though seldom reported, are rather common. Reese [1] in 1934 made a survey of 30 cases of orbital masses and found that 50% of the patients had had exenteration of the orbit for a supposed primary neoplasm which was proved histologically to be a chronic inflammatory tissue mass. The scarcity of such records was brought out tersely by Robinson,[2] in 1947, who reported the first recorded case from New Zealand. It had all the characteristics, both clinically and pathologically, of a pseudotumor.

## ETIOLOGY

The cause of inflammatory pseudotumors of the orbit is unknown. There is no clinical or histologic evidence to prove that the lesions are tuberculous. Some observers believe they are due to late syphilis with a negative Wassermann reaction. Even though there have been reports of regression of the exophthalmos under antisyphilitic therapy, the results probably have been due to the absorptive qualities of the drugs used rather than to a specific action. The histologic picture is not inconsistent with syphilis, particularly the changes in the blood vessels, but there is much other evidence that fails to substantiate syphilis as the etiologic agent.

Williamson-Noble [3] believed that these conditions might be due to a prolonged and excessive manifestation of lymphocytic infiltration following a slight bacterial

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From The Clinic.

1. Reese, A. B.: Symposium: Etiology of Exophthalmos; Complications; Causes from Primary Lesions in the Orbit; Surgery, Tr. Am. Acad. Ophth. **39**:65, 1934.

2. Robinson, W. J.: Pseudo Tumors of the Orbit, Tr. Ophth. Soc. New Zealand, 1947, pp. 18-30.

3. Williamson-Noble, F. A.: Inflammatory Pseudotumor of the Orbit, Brit. J. Ophth. **10**:65 (Feb.) 1926.

invasion. Trotter believed that they are due to lymphatic obstruction, but Wolff [4] denied the existence of true lymphatics in the orbit. Although an actual infectious basis cannot be proved, many case reports are available in the literature which seem to indicate that some time previously the authors were able to uncover an infectious process, other etiologic factors having been ruled out.

### HISTOLOGY

Pathologically, inflammatory pseudotumors of the orbit present chronic inflammation with certain distinguishing characteristics. There may be fibroblastic repair in all stages, from the dense, hyaloid, almost anuclear tissue, of long standing, to the delicate fibroglia and rich nuclear tissue of more recent production. Foci of lymphocytes are scattered throughout the tissue, and occasionally real lymph follicles with germinal centers are encountered. The blood vessels are plentiful, their intima often showing proliferation to such an extent that the lumen appears occluded, and their media and adventitia thickening and sclerosis, perhaps with hyaline degeneration.

### CLASSIFICATION

Classification of these masses in general was made by Birch-Hirschfeld and reported by Williamson-Noble.[3] He defined three classes. In Class I are placed those tumors which are diagnosed but which undergo spontaneous recovery or recovery with the use of potassium iodide, mercury, quinine, or any absorptive agent. In Class II are placed those in which masses are diagnosed but are not found on surgical exploration. In Class III are placed those which macroscopically appear to be true neoplasms but which microscopically prove to be pseudotumors.

### SIGNS AND SYMPTOMS

In a group of cases of pseudotumors analyzed by Reese and others, certain characteristics were found which help to catalogue this entity. Primary among these was exophthalmos. The proptosis was of only moderately rapid development, averaged about 7 mm., and was not accompanied by any signs of inflammation. In about one-half the cases a palpable mass is felt in the orbit. This mass is usually discrete, firm, and well demarcated. Vision is affected in about two-thirds of the cases but usually returns to normal after regression.

Occasionally there is transitory chemosis of the lids for some weeks before the onset of the other symptoms. Paresis of extraocular muscles is very common, and its extent depends on the location of the tumor. One situated in the apex is more likely to give widespread symptoms than one lying just posterior to the globe. Loss of vision is accompanied by engorgement of the venules, hemorrhages of the retina, and/or choking of the disk. The blood picture is not abnormal. There is no leucocytosis, elevation of temperature, or other sign of acute infection of the orbit. There is usually loss of motion of the globe with lateral, as well as anteroposterior, displacement. Complete regression of the mass without treatment may take place in four or five months and may continue to a state of enophthalmos, with sinking of the tarso-orbital fascia. The condition is never recurrent in the same eye.

4. Wolff, E.: Anatomy of the Eye and Orbit, Including the Central Connections, Development, and Comparative Anatomy of the Visual Apparatus, Ed. 3, Baltimore, The Blakiston Company, 1948, pp. 327-338.

DIFFERENTIAL DIAGNOSIS

There are certain general diagnostic points of importance in differentiation of primary tumors and pseudotumors. The average age of patients with pseudotumor is 45 yr. Neoplasms rarely occur after the second decade. The onset of the exophthalmos with neoplasms is insidious. With pseudotumors the onset is relatively sudden, in most instances occurring within a period of several weeks. Pseudotumor of the orbit is rarely bilateral at first, but in over one-third of the cases the condition affects the opposite eye within four to nine months after the onset. Pseudotumors do not produce characteristic roentgenologic changes in the orbital bones. Neoplasms usually cause no pain and no chemosis of the conjunctiva or swelling of the lids, but in over one-half the cases of pseudotumors these symptoms are present. The differential diagnosis of a specific pseudotumor and other orbital masses is both perplexing and interesting.

*Chronic Orbital Myositis.*—Perhaps the most confusing differential diagnosis is that of pseudotumor and the condition reported by Dunnington and Berke,[5] which they called chronic myositis of the orbit of unknown origin. This is a nonspecific chronic inflammatory disease of the extraocular muscles, characterized histologically by lymphocytic infiltration, fibrosis, and degeneration of muscle fibers. Grossly, the muscles are pale and enlarged and have a cartilaginous "feel" when they are cut. Clinically, the condition is characterized by painless edema of the lids of gradual or sudden onset, moderate to severe exophthalmos with limitation of the ocular motions, especially upward, and pronounced inelasticity of the muscles, as shown by the traction test. Because of the exophthalmos and the restriction of ocular motion, the authors have devised the traction test as a differential diagnostic point. In brief, they carry out the test as follows: Assuming that there is marked limitation of upward gaze of one eye, they anesthetize the eye, and then, taking firm hold of the antagonistic muscle, they attempt to elevate the eye in the direction the paralyzed muscle should work. If they find there is no limitation of the ocular rotation in this direction, they feel confident that the muscle is paralyzed; but if there is pronounced resistance to the rotation of the globe, they assume that it is because the paretic muscle is swollen and edematous and occupies more space than normal. In many of these cases biopsy is necessary before a differential diagnosis can be made, but the authors caution against this because the muscle tissue apparently does not heal well after removal of the specimen. In cases of this condition there is likely to be no visual disturbance, as with a pseudotumor, and the x-ray picture shows a slight increase in soft tissue, which is not common in cases of pseudotumor.

*Orbital Apex-Sphenoid Fissure Syndrome.*—The next most difficult differential diagnosis is that of pseudotumor and the "orbital apex-sphenoid fissure syndrome," first reported in the American literature by Holt and de Rötth.[6] This syndrome is due to an inflammatory, a neoplastic, or a traumatic process involving the structures traversing the sphenoidal fissure—that is, the third, fourth, and sixth cranial nerves, the ophthalmic division of the fifth cranial nerve; sympathetic nerves, and the optic

5. Dunnington, J. H., and Berke, R. N.: Exophthalmos Due to Chronic Orbital Myositis, Arch. Ophth. **30**:446 (Oct.) 1943.

6. Holt, H., and de Rötth, A.: Orbital Apex and Sphenoid Fissure Syndrome, Arch. Ophth. **24**:731 (Oct.) 1940.

nerve at the orbital apex. The symptoms of this disease are ptosis, diplopia, partial or complete ophthalmoplegia, wide pupil with loss of reflexes, hyperesthesia or anesthesia in the distribution of the first branch of the fifth cranial nerve, and severe optic neuritis, with later optic nerve atrophy. Pain is an early symptom; it is localized behind the eyeball and radiates to the temples. Exophthalmos is inconsistent and slight. The syndrome is complete when all the nerves in the region, including the optic nerve, are involved. If the process is limited to the sphenoidal fissure, the optic nerve is spared. There may be involvement of only the external and intrinsic muscles of the eye, without involvement of the fifth cranial or the optic nerve; or the limitation may comprise only the third cranial nerve and the parasympathetic nerve fibers. The differential diagnosis cannot be made on symptoms alone; it is made from roentgenograms of the sphenoidal fissure, which show in cases of the sphenoidal syndrome a marked periostitis of the sphenoidal fissure and optic foramen. This results in narrowing of the involved fissure.

*Neoplastic Tumors.*—Bony tumors of the orbit should present no difficulty as the appearance in the roentgenogram of both exostoses and enostoses is rather prominent. The carcinomas, sarcomas, hemangiomas, and lymphomas, secondary to sinus involvement, likewise give otolaryngologic and roentgenologic findings. Mucocele and angioneurotic edema must be differentiated, partially from the history and partially from the physical findings. The nasopharyngeal tumors, so common among the Chinese population of Hawaii, with metastases to the orbit, are differentiated on an otolaryngologic basis.

*Thyrotoxicosis.*—There should be little difficulty in distinguishing thyrotoxic exophthalmos from a pseudotumor. The bilateral involvement, together with the slight limitation of motion and the fact that the exophthalmos is usually in an anteroposterior plane, distinguish the former condition. The low blood cholesterol, the high basal-metabolic rate, the elevated pulse rate, and the disturbance of the temperature center are all distinguishing features.

*Pituitary Exophthalmos.*—The differentiation of a pseudotumor of the orbit from exophthalmos of a thyrotropic disturbance presents quite a different, and a more difficult, problem. In the latter, the hormone of the anterior lobe of the pituitary responsible for the disturbance produces an entirely different pattern. The usual signs of thyrotoxicosis are missing; there is no disturbance of the sympathetic nervous system to account for the prominent exophthalmos, due to contraction of Müller's muscle, so that the exophthalmos in these cases might easily simulate that of a beginning inflammatory pseudotumor, and probably more of the thyrotropic cases than of the thyrotoxic group are diagnosed. Pathologically, a quite different picture exists in this condition. In thyrotropic exophthalmos, the extraocular muscles are greatly increased in size and microscopically show much fibrosis of the fibers, inter- and extra-fibrillar edema, muscle degeneration, and round-cell infiltration. The pathologic picture closely simulates that of chronic myositis of unknown origin, as reported by Dunnington and Berke.

Naffziger [7] stated that it is clear from clinical experience that marked and progressive proptosis is not of necessity associated with hyperthyroidism, but

7. Naffziger, H. C.: Progressive Exophthalmos Following Thyroidectomy, Pathology and Treatment, Ann. Surg. **98**:582 (Oct.) 1931.

oftener accompanies hypothyroidism, and that there is clinical and experimental evidence that the pathologic relationship of the thyrotropic hormone and the exophthalmos is a very close one.

### CLASSIFICATION OF ORBITAL TUMORS

Samuels[8] divided tumors of the orbit into five groups. In Group 1 are those producing intense inflammatory reaction in the surrounding tissue, which is due to the slowness of the growth of the tumor. Of this class, carcinoma is the best example. These tumors have a strong tendency to invoke an inflammatory reaction adjacent to the growth, with the formation of new fibrous tissue and displacement of the globe, due to the scar. Cylindromas originate in the lacrimal gland and such tissue misplaced in the orbit and resemble basal-cell carcinoma in form; they, too, produce a scirrhous reaction.

In Group 2 are classified tumors which do not cause an inflammatory reaction and are, therefore, of more rapid growth. The sarcomas are the most frequent of these tumors and are usually encapsulated.

Group 3 includes tumors of the optic nerve, the endotheliomas, which are rare, and the gliomas. Gliomas of the optic nerve may result in a rather striking preservation of vision for a long time, because the optic nerve fibers are able to traverse the gliomatous mass.

Group 4, probably the most important group to be differentiated from pseudotumors, is composed of tumors invading the retro-orbital space from within the globe. The most important of these is sarcoma of the globe.

Lastly, in Group 5 are the inflammatory pseudotumors of the orbit, which must be differentiated from all the preceding types. The diagnostic points of a rather sudden onset of the exophthalmos, the finding of an infectious origin in the body, the presence of a primary tumor elsewhere in the body, and an unusual disturbance in the fundus picture, all help to differentiate these from the aforementioned tumors.

### TREATMENT

Many surgeons suggest that if a diagnosis can be made and the surgeon has the courage to keep the patient under observation until permanent damage is sure of developing, a long period of watchful waiting be observed. There are, however, many "ifs" in this creed, and strict adherence to it is very trying. In this era of 'mycin's and 'illin's, it is most natural to institute a complete course of whatever seems to the surgeon most applicable at the time. When the disease is justly confused with a thyrotropic disturbance, thyroid therapy will probably help. X-ray therapy has its advocates. I am convinced that unless deep therapy is given immediately and in sufficient dosage, little or no effect on the course of the disease can be expected.

Conservative surgical treatment, so far as the globe is concerned, must be exploratory. Some prefer the orbital approach, which is excellent for lesions in the anterior third of the orbit; others prefer the transcranial approach, which seems ideal when the lesion is suspected of being near the apex of the muscle cone or when there is a possibility of its being primary in the anterior fossa with extension through the optic foramen. There are still advocates of the Krönlein approach,

8. Samuels, B.: Tumors of Conjunctiva and Lids: Brief Review, Arch. Ophth. **26**:789 (Nov.) 1941.

but they are becoming fewer as the years go by, partly because of the disfiguring scar and partly because of the ease with which the other two approaches can be made.

Jackson [9] cited the following advantages of the transfrontal approach to pseudotumors of the orbit: (1) The approach is more direct and more adequate; (2) any intracranial extension is easily followed; (3) there is less interference with ocular motility; (4) there is no ugly scar; (5) there is no possibility of a pulsating scar, and (6) the risk, with modern chemotherapeutic agents on hand, is no greater than that of any other approach.

Benedict,[10] of the Mayo Clinic, admonished that if a biopsy specimen is taken, it should be a good one and a careful frozen section should be made at the time.

Lewis [11] decried the scarcity of reports of cases of these tumors in the literature. He stated the belief that a course of x-ray treatments is indicated and that if biopsy reveals an inflammatory pseudotumor the physician should assure the patient that he will recover, so that he will not acquire a "tumor phobia."

## REPORT OF A CASE

F. D., a white man aged 24, was seen on March 16, 1950, with the complaint of a dull frontal headache of about two months' duration. He also complained of slight pain in the region of the left eye and the left side of the forehead. He stated that the pain was worse at night, and apparently worse when the weather was cool and on cold nights. At times it was so severe at night that it awakened him. The pain was increased on exertion. His past history and family history were noncontributory. He had been given refraction and glasses prescribed, with no apparent relief. A stereoscopic roentgenogram of the skull had shown nothing abnormal, and a tentative diagnosis of trigeminal neuralgia had been made.

During the first physical examination, it was noticed that there were two false upper incisor teeth, the originals having been extracted because of an alveolar cyst. A letter from the dentist follows: "On Feb. 10, 1949, the patient came to me complaining of pain in the upper left facial region. I took several x-ray pictures and found a large serous cyst involving two teeth. On Feb. 14, I removed the two teeth and a cyst, which had perforated the hard palate and extended into the nose. I kept the cavity open with gauze packs for some time. Roentgenograms taken 15 and 72 days after operation are as shown." Our roentgenologist reported that the roentgenogram taken at 72 days showed good filling in of the margins and some callus formation.

Neurologic examination on the first visit revealed an entirely normal condition. Because the neurologist considered that the pain might be on the basis of a sinus infection, roentgenograms of the sinuses and the skull were again taken. The roentgenologist's report at this time was as follows: "The skull plate was normal. The sella was normal in size and shape. The inner glenoid ligaments showed partial calcification. The pineal gland was calcified and in normal position. The paranasal sinuses and mastoids were normal." The otolaryngologist's report on the same date was as follows: "There were a marked septal deviation to the left and slight nasal congestion on the right. The patient stated that an irrigation of the left antrum had been done recently, with apparently negative results."

A few days later the patient returned, and at that time it was noticed that the left temporal artery was prominent and pulsated considerably. The region of the left temporal artery was injected with procaine, which gave him complete relief of pain for about two hours. At this time, 25 mg. of diphenhydramine (benadryl®) hydrochloride, three times a day, was prescribed.

9. Jackson, H.: Orbital Tumors, Proc. Roy. Soc. Med. **38**:587 (Aug.) 1945.

10. Benedict, W. L., and Knight, M. S.: Inflammatory Pseudotumor of the Orbit, Arch. Ophth. **52**:582 (Nov.) 1923.

11. Lewis, P. M.: Inflammatory Pseudotumor of the Orbit: Report of Case, Am. J. Ophth. **21**:991 (Sept.) 1938.

A notation by the neurologist at this time stated that the condition might be a temporal arteritis, a diagnosis which at this time seemed very logical, and that if the pain was again relieved with injections of procaine it would be wise to do an excision of a portion of the temporal artery.

The patient was not seen again until April 11, 1950, at which time he was still complaining of pain in the left eye, the left side of the forehead, and the left temporal region and had just begun to experience double vision. Neurologic examination again revealed an entirely normal condition except for diplopia, and the Wassermann reaction at this time was negative. The patient was referred to me on April 12.

The ophthalmologic report on this date was as follows: "Vision was 20/20 in each eye. Disconjugate motion of convergence was within normal limits. Pupillary reactions were normal to light and in accommodation. There was no marked limitation of voluntary ocular motion in any field except for very slight weakness in the field of rotation of the left external rectus, and then only on extreme lateral gaze. The cover test showed left hypertropia combined with esotropia. The red-glass diplopia test showed weakness of the right inferior oblique and the left external rectus muscles."

Examination the following day showed nothing new. There were still no neurologic changes. Another roentgenogram of the sinuses revealed nothing abnormal. A complete blood count showed 16,000 white cells, with no other abnormality. The urine was normal.

Because of the possibility of an obscure virus infection, aureomycin was given orally for five days, with no apparent relief.

On April 18, six days later, the red-glass diplopia test again showed about the same degree of muscle weakness. The patient was not complaining of homonymous diplopia. Thirteen days later the patient volunteered the information that the two images of the diplopia picture were then much closer together. He was feeling much better and was working in the office again. On the same day, however, red-glass diplopia tests showed that, in addition to weakness of the left external rectus and right inferior oblique, there was beginning slight paresis of the left external rectus muscle. He spontaneously gave the information that he was glad to keep the left eye patched and that a pressure patch gave him considerable relief from the pain and enabled him to work four or five hours a day.

On May 2, the diplopia test showed involvement of the same three muscles. The patient was now complaining bitterly of pain in and around the eye; he looked ill and was eager to go to the hospital. A complete blood count at this time showed 13,000 white cells, 70% polymorphonuclear leucocytes, and a normal red cell count. There was no shift to the left. A roentgenogram taken at this time showed some absorption of bone around the optic foramen. A consulting ophthalmologist was unable to find any additional sign of beginning neuritis of the left optic disk. A spinal puncture showed a pressure of 210 mm., without block. Seven cubic centimeters was removed, with a final pressure of 190 mm.

Six days later the ophthalmologic picture had changed considerably from any of the previous ones. He then had rather pronounced paresis of the external rectus, internal rectus, superior rectus and inferior oblique on the left side, with partial ptosis and a suggestion of proptosis. The fundus picture revealed prominent distention of the venules with deepening increase in the color, signs of compression where the veins were crossed by the arterioles, 3 D. of choking of the nerve head, and obscuring of the superior nasal margin of the disk of the right eye. I suggested angiographic studies to rule out a possible aneurysm, in spite of the absence of a bruit and any demonstrable change in the caliber of the venules on compression of the carotid artery. The spinal fluid at this time was reported as showing a total cell count of 23 and a total white cell count of 15 per cubic millimeter; a total protein content of 44.2 mg. per 100 cc., a normal sugar level, a flat colloidal mastic curve, and a negative Wassermann reaction with 1 cc. of fluid.

Dr. R. B. Cloward, in consultation, agreed that angiographic studies were indicated. These, made via the left internal carotid artery, showed fairly good filling and visualization on the arterial side. The distribution of the vessels appeared grossly normal.

On May 11, red-glass diplopia fields again showed paralysis of all the extraocular muscles on the left side with the exception of the external rectus muscle. The direct and consensual pupillary reactions were still normal. The edema of the disk was unchanged. There was no progression of the neuritis on the right side.

At this time I believed that the lesion was at the orbital apex and was of either inflammatory or neoplastic nature. However, I was at a loss to explain why there was no proptosis. The radiologist did not agree that there were any changes in the optic foramen. At this time, penicillin therapy was started, 600,000 units being given intramuscularly each day, and was continued for 10 days. The rationale for this treatment was the assumption that the condition was on an inflammatory basis, and I wanted to rule this out, if possible.

On May 13, a pneumoencephalogram showed that the lateral ventricles were in the midline and normal in size, but slightly asymmetrical, the left being larger than the right. The third ventricle was well filled and lay in the midline. The entire cortical subarachnoid pathways showed rather marked dilatation, the sulci averaging 3 to 4 mm. in width, suggesting generalized cortical atrophy.

At the end of 10 days of penicillin therapy, which did not affect the course of the disease, the diagnosis of a sphenoidal fissure syndrome, due to inflammatory periostitis of the sphenoidal fissure, was considered. This seemed to be a logical explanation for the extensive nerve involvement and the choking of the disk without proptosis. It was believed that if there was a retro-orbital mass of any size, such a space-taking lesion certainly would produce definite proptosis by this time.

Roentgenograms of the sphenoidal fissure, however, were reported to show no abnormality. Probably because my colleagues and I were now convinced that the lesion must be on an inflammatory basis, 450 r of filtered x-rays was given, directed to the orbital apex. The fundus picture at this time showed a much higher degree of choking, greater extension of the venules,

Fig. 1.—Patient just prior to exenteration of the orbit.

and some deep hemorrhages and small exudative areas on the nasal aspect of the disk. Vision was then 5/200 in the affected eye. The exophthalmometric recordings were again within 1 mm. of each other, but the left eye was displaced downward and outward. The intraocular tension was normal on both sides.

X-ray therapy did not cause any decrease in the symptoms, and on June 5 the following surgical procedure was carried out:

The left orbital plate was exposed in the usual manner. An L-shaped incision was made in Tenon's periorbital capsule extending down to, and including, the dural cuff of the optic nerve. Prior to the opening of the orbital capsule, palpation showed the intraorbital contents to be under considerable pressure, with pronounced herniation when the capsule was opened.

Palpation of the orbit revealed a stony-hard mass projecting upward from the floor of the orbit, giving one the impression of a bony ridge. Careful dissection superiorly, both lateral and medial, failed to disclose any abnormality.

By retraction of the ocular muscles and the optic nerve, a circumscribed, glistening, silvery-gray mass was isolated. It was approximately 2.5 by 1 cm. and was shaped like a bullet. The apex was situated at the confluent attachment of the extraocular muscles. The blunt end of the mass extended anterior to the globe. The tumor was tightly adherent to the floor of the orbit, requiring considerable force and some sharp dissection to dislodge it. It was removed in toto, however, leaving a clean bed. No damage except that due to forceful retraction was done to the surrounding ocular muscles or nerves, and no intraorbital hemorrhage occurred in the dissection. The bleeding points over the dura mater were arrested with gelfoam® and cautery.

Forty cubic centimeters of spinal fluid was replaced in the spinal canal, reexpanding the frontal lobe. The bone flap was replaced and secured with one stainless-steel wire. Trephine

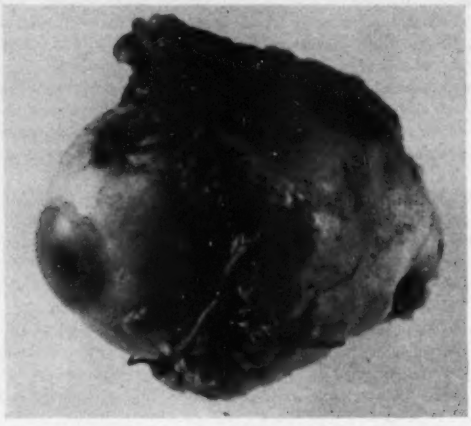

Fig. 2.—Gross section of the eye removed at operation.

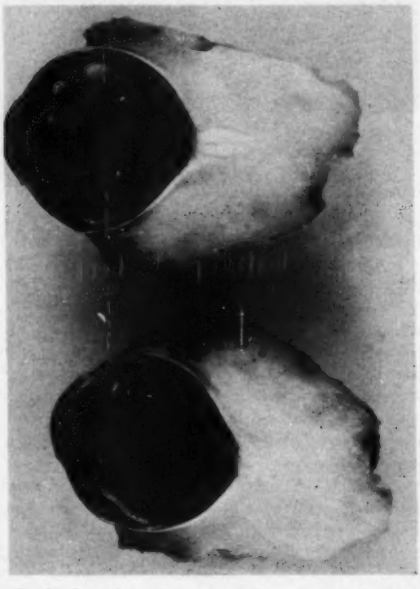

Fig. 3.—Sagittal section of gross specimen removed at operation.

holes were filled with bone dust. The scalp was replaced and closed with two layers of black silk sutures. The postoperative condition was good.

*Pathological Report.*—Gross Examination: The specimen consisted of nine irregular fragments of tissue said to have been removed from the retrobulbar area. These fragments varied from 2 to 5 mm. in length. They appeared to consist mostly of fibrofatty tissue. One of these segments appeared to have an outer capsule, and beneath was homogeneous, firm white tissue.

Microscopic Examination and Diagnosis: The specimens submitted all showed a similar picture, which was one of tissue made up of a fibrous or connective tissue stroma with dark-staining fibroblasts, which showed a certain amount of degeneration. Some muscle fibers were intermingled with the muscle tissue. A few nerves, cut in cross and longitudinal section, were also present. Some of the small sections showed a few scattered inflammatory cells. One of the small particles was made up of fibrous and fat tissue. In the stroma between the fat tissue

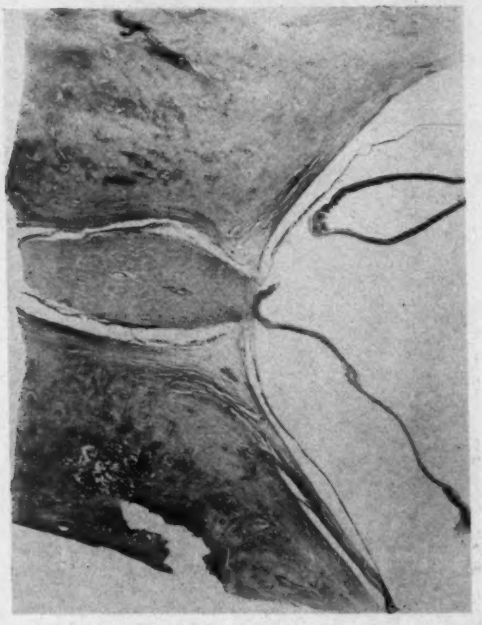

Fig. 4.—Low-power microphotograph of the tumor mass.

numerous polymorphonuclear neutrophils were present. There was nothing in the section to indicate a neoplasm.

The tentative diagnosis was nonspecific inflammation in tissue from the retrobulbar area.

Further section of the rest of the tissues revealed a similar picture of fibrous connective tissue with a group of nerves cut in transverse section. Focal collections of chronic inflammatory cells, mostly lymphocytes and plasma cells, were present. There was no evidence of neoplasm.

The final diagnosis was chronic inflammation in tissue from the retrobulbar area.

*Further Course.*—The patient was next seen on Aug. 2, at which time he complained of a slight return of the original pain over the left side, with swelling of the upper left lid; he volunteered the information that the ptosis was worse than it had been three weeks before. Vision was equal to counting fingers at 1 ft. (30 cm.). The pupil was semidilated and fixed. There was then 2 mm. of exophthalmos, as measured by the Hertel exophthalmometer. There was approximately 5 degrees of external rotation of the left eye. The fundus showed optic nerve

atrophy, 3 plus. The venule-arteriole ratio was 4:2. There were no hemorrhages, but lines of retinal edema radiated out about 2 disk diameters from the disk. Pictures of the sphenoidal fissure were again taken and reported to show nothing abnormal. Administration of potassium iodide, 5 minims (0.308 cc.), with an increase in dose of 1 minim (0.062 cc.) daily, was now instituted and the eye patched. The patient then, as always, felt better when the eye was patched.

On Sept. 8 the patient was seen again. Because the patient lived on another island and preferred to return home for intervals, our examination dates were distantly spaced. At this time tension was normal; the pupil was dilated and fixed, and there was about 5 degrees of external rotation. A definite resistance to backward pressure of the globe was felt. There was marked enlargement and engorgement of the circumlimbal superficial vessels, resembling a

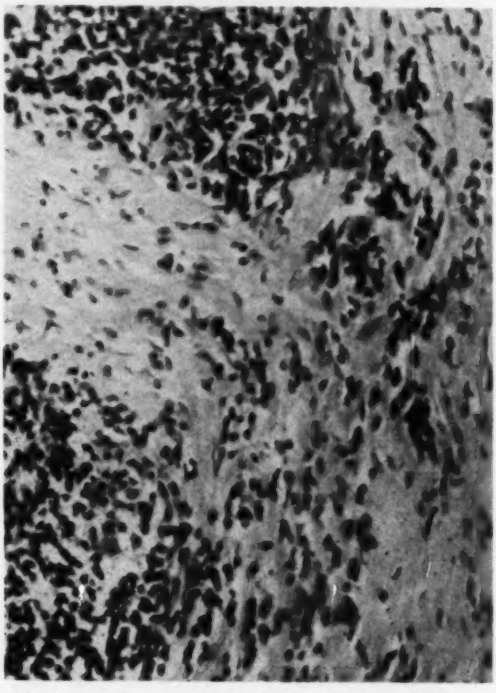

Fig. 5.—Medium-power microphotograph of section of the tumor mass.

caput medusae. The fundus showed the previous picture of optic nerve atrophy and a rather typical picture of thrombosis of the central retinal vein, linear hemorrhages accompanying practically all of its subdivisions. A flat retinal detachment also occupied the lower half of the globe.

On Sept. 29 the left globe was displaced downward and outward. The pupil was dilated and fixed. Tension was still normal. The Hertel exophthalmometer reading was 10 mm. for the right eye and 17 mm. for the left eye. Many of the hemorrhages had absorbed, and the retinal detachment was much flatter. At this time exenteration of the orbit was advised. We were convinced that return of vision was improbable and that a malignant change in the orbital contents was a probability to be kept in mind. A complete blood study at this time, including determination of the sedimentation rate, again gave normal results. The preoperative diagnosis was, first, pseudotumor of the orbit, inflammatory in nature, and, second, a malignant growth involving the orbital contents.

On Oct. 25, an exenteration was performed with the patient under thiopental (pentothal®) sodium anesthesia. The procedure was as follows:

A wide canthotomy was made bilaterally. The conjunctiva was incised completely around the limbus and reflected back to the orbital rim. An incision was then made beneath this conjunctiva completely around the orbital rim. The periorbita was then loosened completely around and its dissection carried out back to the orbital apex in all areas except the superior portion, where it was incised 10 mm. from the rim in the region where the superior orbital plate was missing, a result of the previous operation. Dissection was continued inside at this point because of the adhesions between the periorbita and the dura. Delivery of the globe and its contents encountered considerable difficulty, but was finally accomplished, without excessive bleeding. There was a small perforation of the inferior orbital wall, but the lining of the maxillary sinus had not been perforated. The lacrimal sac was not disturbed. After the delivery of the globe and its contents, some of the thickened periorbita overlying the dura was trimmed away. Plasma and thromboplastin were used in the socket, and the socket was packed with gauze soaked with sulfacetimide ointment, care being taken to spread the ocular conjunctiva over as great an area of the socket as possible, particularly over the dural area. Canthotomy wounds were closed with plain O surgical suture U.S.P., and a pressure bandage was applied. The postoperative condition was satisfactory.

A portion of the specimen was forwarded to Dr. W. L. Benedict,[12] who reported the sections to show a chronic inflammatory pseudotumor.

Postoperative recovery was uneventful; all the packing was removed and a conformer placed in the socket on Nov. 3.

Fig. 6.—Postoperative result with prosthesis in place and crutch on the lens before the left eye.

The patient did not return until Feb. 2, 1951, at which time there was an inversion of the lower lid in the region of the external canthus, where it had been drawn in by adhesions in the shrinkage of the conjunctival lining of the socket. A small amount of granulation tissue was present at the very apex of the socket; otherwise, the bony cavity had become well epithelized.

With the patient under thiopental sodium anesthesia, the canthus was freed from the conjunctival adhesions; a small full-thickness graft of buccal mucous membrane was inserted over the raw surface; the granulation tissue was removed, and its base was cauterized with 25% silver nitrate.

On Feb. 8, the patient was discharged to his home with conformer in place and was placed under the care of his local physician, who was instructed to keep down granulations and to make sure the patient wore the conformer.

At the time of this report, the socket has completely epithelized; the permanent prosthesis is in place, and the patient is wearing a ptosis crutch on the left side. He has a good cosmetic result, and no indication of the development of a similar process in the opposite eye is evident.

## COMMENT

The original diagnosis of the referring physician was trigeminal neuralgia, for which he had sufficient evidence. During the next few days, it was thought that the condition might be a virus infection, since such a bizarre picture had recently been seen by an associate and had been materially helped with the use of aureo-

12. Benedict, W. L.: Personal communication to the author.

mycin. Then the picture of temporal arteritis came into view, and because the symptoms were strikingly relieved by the injection of procaine into the temporal artery this diagnosis could not be passed over lightly. However, with the progression of symptoms and failure of any of the past treatments to change the picture, the possibility, first, of an intracranial aneurysm and, second, of an intraorbital aneurysm was considered. In due course of time these two possibilities were also ruled out.

The most probable diagnosis, and the hardest to rule out, was the sphenoid fissure syndrome, and it was only because of the repeated negative roentgenologic reports that we were able to conclude that this was not the proper diagnosis.

The conclusion that the lesion was an inflammatory retrobulbar mass was reached through a process of elimination.

## SUMMARY

Pseudotumors of the orbit are briefly discussed. A case is reported, its course being followed from the appearance of the first signs, through the clinical, surgical, and postoperative phases, to the final stage of cure, with a good cosmetic result.

# BILATERAL INTERNAL CAROTID ANEURYSM INVOLVING CAVERNOUS SINUS

## Right Carotid Artery-Cavernous Sinus Fistula and Left Saccular Aneurysm

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AND
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BILATERAL aneurysms involving the internal carotid artery in the cavernous sinus are rare and present difficulties in diagnosis and treatment. Among 75 verified aneurysms, only a single instance of such an aneurysm has been encountered. For this reason the case here reported appears to be significant.

### REPORT OF A CASE

*Bilateral aneurysm of cavernous sinus; carotid artery-cavernous sinus fistula on right and saccular aneurysm on left.*

*History.*—M. L. (J. H. #NH8890), a woman aged 45, was transferred to the Jefferson Medical College Hospital from the service of one of us (I. M. T.) in the Wills Hospital on Dec. 2, 1950. She had been well until about five weeks before admission (Oct. 30), when she suddenly experienced a dizzy spell while undressing for bed. She described this episode as a "sinking, swimming sensation," from which she had suffered from time to time in the past. As a result of one of her subsequent dizzy spells, four days before admission, she fell to the floor, striking the vertex and left temporoparietal region. She was dazed but not rendered unconscious; on arising from the floor, she became aware for the first time of severe, pounding left frontotemporal headache. Within a few minutes her left eye became swollen and her eyelid completely closed. The headache continued during the following week, and her eyelid remained swollen and closed. On several occasions during this period she lifted her eyelid and found that she was unable to move her eyeball. Hot packs relieved the swelling but failed to improve the mobility of the eyeball.

Three days after the onset of her trouble (Dec. 1), while standing at a window gazing out into the street, she experienced severe, throbbing pain in the right frontotemporal region associated with nausea and vomiting. The following morning, on arising, she became aware of a noise in her head, and during that day swelling and ptosis of the right eyelid and prominence of the right eyeball occurred.

The past history disclosed recurrent headaches, lasting one to two days, in the premenstrual period and relieved by acetylsalicylic acid. In December, 1949, about 11 mo. before appearance of her present symptoms, there developed weakness, but not complete paralysis, of the left arm, clearing up in about two months. Two to three years before onset of her present illness she experienced a noise in her head, which persisted until six weeks before the onset of the trouble which brought her into the hospital. She described the noise as sounding like machinery, heard in all parts of her head and more pronounced when her blood pressure was elevated.

From the Wills Hospital and the Department of Neurology, Jefferson Medical College of Philadelphia.

Neurological examination revealed bilateral exophthalmos, more pronounced in the right eye. On neither side was there pulsation of the eyeball. There was pronounced edema of the eyelids. There were complete ptosis of the left eyelid with complete immobility of the left eyeball, a dilated left pupil with loss of reaction to light and in accommodation, and loss of the left corneal reflex with hypalgesia over the supraorbital division of the left trigeminal nerve. The

Fig. 1.—Photographs of the patient, demonstrating the bilateral ophthalmoplegia.

Fig. 2.—On the right (*A*) is seen the carotid artery-cavernous sinus aneurysm, and on the left (*B*), the saccular aneurysm involving the cavernous-sinus portion of the internal carotid artery.

right pupil was small and failed to react to light and in accommodation. The right eyeball was completely immobile and failed to move in any direction (Fig. 1). The right corneal reflex was lost. No changes were found in the fundi, the optic nerves being well defined and of normal color. Visual field studies performed in the Wills Hospital revealed normal fields for form and color, with no scotoma and no enlargement of the blindspots. Apart from the ocular findings, there were no changes to be observed on routine neurological examination. A loud bruit was

heard over the entire right side of the skull, being most pronounced over the right eye and the right side of the face, but heard faintly over the vertex and the vessels on the right side of the neck. It was completely obliterated by compression of the carotid vessels in the right side of the neck.

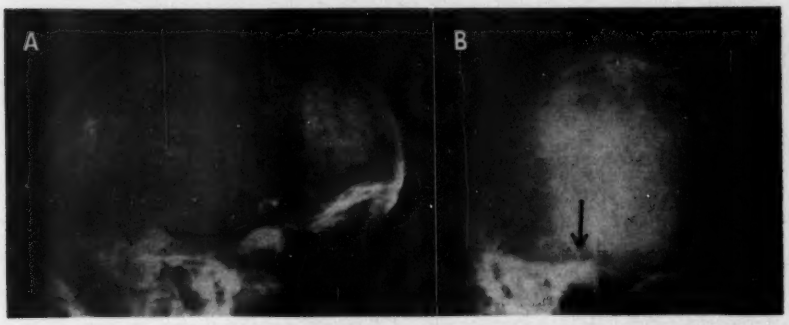


Fig. 3.—A lateral view (*A*) of the carotid artery-cavernous sinus aneurysm and an anteroposterior view (*B*) of the same aneurysm.

Fig. 4.—Photographs of the patient before development of right ophthalmoplegia (*A*) and prior to her discharge from the hospital (*B*).

*Laboratory Studies.*—The urine was normal except for a specific gravity of 1.012, a trace of albumin, and an occasional red blood cell. Studies of the blood revealed 11 gm. of hemoglobin per 100 cc., 3,620,000 erythrocytes, and 4,500 leucocytes with a normal differential count. The blood urea nitrogen was 9.2 and 4.8 mg. per 100 cc. on two occasions. The Wassermann and

Kahn reactions of the blood were negative. Spinal fluid studies were not made. Roentgenograms of the skull revealed demineralization of the dorsum sellae and the floor of the sella turcica. The right anterior clinoid process was described as being shortened and different from the left.

Arteriographic study with thorotrast® was performed on Dec. 6, by Dr. William H. Whiteley. On the right side there was noted a huge, diffuse dilatation of the internal carotid artery just before its bifurcation into the anterior and middle cerebral vessels (Fig. 2). On the left side the arteriogram revealed a saccular aneurysm arising from the lateral aspect of the internal carotid artery about 1 inch (2.5 cm.) before its bifurcation into the anterior and middle branches (Fig. 3).

*Summary.*—In this case, that of a woman aged 45, a bilateral cavernous-sinus aneurysm developed against a background of premenstrual headache extending over a number of years. She was known to have hypertension, and about 11 mo. before the onset of her present illness she had weakness of the left arm, lasting about two months. Two or three years previously she experienced a noise in her head, which persisted until six weeks before her present trouble. About five weeks before her entrance into the hospital she experienced severe headache and complete ophthalmoplegia on the left side, followed in 30 days by headache and ophthalmoplegia on the right side. Examination revealed bilateral exophthalmos, greater on the right, with complete ophthalmoplegia bilaterally. A loud bruit was heard over the right side of the face and head. Arteriographic studies revealed a carotid artery-cavernous sinus fistula on the right side and a saccular aneurysm on the left. During the course of her hospital stay the patient recovered partial use of the right eye. She was discharged without operation. Review of her problem five weeks after discharge revealed complete return of movement of the right eyeball except for residual paralysis of the external rectus. The ophthalmoplegia on the left side remained unchanged. The bruit was still heard over the entire head but was loudest on the right side.

## COMMENT

Bilateral aneurysm of the portion of the internal carotid artery within the cavernous sinus is rare. The case here reported was further unusual in the occurrence in the same subject of a carotid artery-cavernous sinus fistula on one side and a saccular aneurysm on the opposite side. Complete ophthalmoplegia was present bilaterally. Bilateral carotid artery-cavernous sinus fistula, on the other hand, is not uncommon. Sattler,[1] in his extensive monograph on pulsating exophthalmos, found 36 instances among 175 cases of traumatic origin, and 5 among 60 cases of idiopathic origin. He pointed out, however, that the development of a pulsating exophthalmos in the second eye almost never results from rupture of the second carotid vessel but is caused by an overflow of the arterial blood through the intercavernous sinus and through the second cavernous sinus into the venous system of the second orbit. The disorder develops, moreover, in different degrees in the two eyes, being more pronounced in the originally involved eye. The involvement of the second eye may develop a few days, weeks, or months after the original rupture.

Riehm [2] described a case of bilateral carotid artery-cavernous sinus aneurysms which appeared to have developed independently on the two sides over a period

1. Sattler, C. H.: Pulsierender Exophthalmus, in Saemisch, T.: Handbuch der gesamten Augenheilkunde, Ed. 2, Leipzig, W. Engelmann, 1913, Vol. 9, Pt. 2, Chap. 13, p. 25.

2. Riehm, H.: Bilateral Nontraumatic Arteriovenous Aneurysm Between the Internal Carotid Artery and the Cavernous Sinus, with Pulsating Exophthalmos, Deutsche med. Wchnschr. **48**:287 (March 3) 1922.

of six months. Jefferson [3] reported bilateral aneurysms of the portion of the internal carotid artery in the cavernous sinus in a woman aged 72. The aneurysms, whose presence was confirmed at autopsy, were fusiform, the left being larger than the right. Involvement of the carotid arteries by aneurysms in both cavernous sinuses was seen in a woman aged 63 by Mahoudeau, Daum, George, and Rosier.[4] Autopsy revealed a saccular aneurysm of the internal carotid artery on the left side and a fusiform aneurysm of the vessel on the right side. Bilateral aneurysm of the carotid artery and cavernous sinus was described by Dollfus, Taptas, and Brisac [5] in a woman aged 42. Complete ophthalmoplegia, both internal and external, was found in the right eye, and a bruit was heard over the head and chest. The arteriogram was normal, but ligation of the common carotid artery on the right side caused disappearance of the bruit. Three days after ligation of the artery, the patient had paralysis of the abducens nerve and partial paralysis of the oculomotor nerve. No arteriographic procedure was performed on the left side.

The rarity of bilateral aneurysm of the internal carotid artery in the cavernous sinus is attested to by the few reports of such cases in the literature. The instances recorded by Sattler of bilateral pulsating exophthalmos were not due to the independent development of aneurysms on the two sides, but, rather, were the result of the overflow of blood into the uninvolved eye by means of the intercavernous sinus. In the other recorded instances, including the present case, two separate aneurysms involved the eyes at different times, causing ophthalmoplegias of varying degrees of severity. The recorded aneurysms have been carotid artery-cavernous sinus aneurysms (Sattler; Dollfus, Taptas, and Brisac; Riehm); fusiform internal carotid aneurysms (Jefferson), and a saccular aneurysm of one side and a fusiform aneurysm of the opposite side (Mahoudeau, and associates).

The clinical features of bilateral aneurysm of the internal carotid artery in the cavernous sinus vary from case to case. In no instance have both eyes been involved simultaneously. In the case here recorded the second eye was affected 30 days after the first eye (Alpers, Schlezinger, and Tassman). In other instances the intervals have been six months (Riehm) and three days (Dollfus and associates). The ophthalmoplegia may be complete or incomplete in both eyes or complete in one eye and incomplete in the other. The issue of significance is that aneurysm of the internal carotid artery within the cavernous sinus may in rare instances be bilateral and may cause bilateral ophthalmoplegia of varying degree. The aneurysms in question may in some instances be carotid artery-cavernous sinus fistulas; in others, a carotid artery-cavernous sinus fistula on one side and a saccular aneurysm on the other, and in still others a fusiform aneurysm on both sides.

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3. Jefferson, G.: On the Saccular Aneurysms of the Internal Carotid Artery in Cavernous Sinus, Brit. J. Surg. **26**:267, 1938.

4. Mahoudeau, D.; Daum, S.; George, and Rosier: Bilateral Ophthalmoplegia Associated with Bilateral Intracranial Aneurysm of the Internal Carotid Artery, Bull. et. mém. Soc. méd. hôp. Paris **65**:503 (April 1) 1949.

5. Dollfus, M. A.; Taptas, J., and Brisac: Spontaneous Total Bilateral Ophthalmoplegia with the Syndrome of Intracranial Arteriovenous Aneurysm, Bull. Soc. opht. Paris **2**:458 (Nov.-Dec.) 1947.

# CONGENITAL ARTERIOVENOUS (RACEMOSE) ANEURYSM OF THE RETINA

## Report of Three Cases

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CONGENITAL arteriovenous aneurysm of the retina is a developmental anomaly of rare occurrence. The complexity of the retinal changes varies greatly, as does the symptomatology. The essential feature of the ophthalmoscopic picture is a communication between an artery and a vein. This may be duplicated a number of times, with pronounced dilatation of the intervening capillary system. A great increase in the size, shape, number, and tortuosity of the retinal blood vessels may also be encountered. It is impossible in many cases to decide where the dividing line between vein and artery should be drawn. Frequently it is difficult to ascertain whether a vessel is an artery or a vein. The visual acuity is often severely reduced but may be normal. In general there is no progression of the anomaly.

Involvement of the retinal vessels alone, without vascular malformation elsewhere, may occur. The possibility of coexistent arteriovenous aneurysm or vascular malformation in other locations, particularly intracranial, must always be kept in mind. In fact, associated intracranial vascular aberration may account for the many and varied ocular and cerebral signs, such as strabismus, nystagmus, proptosis, bilateral ptosis, paralysis of conjugate ocular movement, hemiparesis, and mental changes, to mention but a few. It is important to note that in the majority of the cases the intracranial vascular lesion is present on the same side as that of the retinal changes.

### REVIEW OF LITERATURE

The reader is referred to an excellent paper on this subject by Wyburn-Mason.[1] The essential features of the cases of arteriovenous aneurysm of the retina in the available literature[2] are summarized in the accompanying table.

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From the Department of Ophthalmic Surgery, University of Michigan Medical School (Dr. Falls).

1. Wyburn-Mason, R.: Arteriovenous Aneurysm of Mid-Brain and Retina, Facial Nævi and Mental Changes, Brain **66**:163, 1943.

2. (*a*) Biró, I.: Racemose Retinal Aneurysm, Ophthalmologica **121**:201, 1951. (*b*) Bonnet, P.; Dechaume, J., and Blanc, E.: L'anévrysme cirsoïde de la rétine (Anévrysme racémeux). Ses relations avec l'anévrysme cirsoïde de la face et avec l'anévrysme cirsoïde du cerveau, J. méd. Lyon **18**:165, 1937; Bull et mém. Soc. franç. opht. **51**:521, 1938. (*c*) Bower, L. E.; Ditkowsky, S. P.; Klein, B. A., and Bronstein, I. P.: Arteriovenous Angioma

## REPORT OF THREE CASES

CASE 1.—A man aged 25, of Japanese extraction, was examined in the ophthalmological clinic at the University Hospital for treatment of a chalazion in the right upper lid. The family history gave no evidence of a similar anomaly and was noncontributory. Visual acuity was 6/6 in each eye with correction. Refraction with cycloplegia (hydroxyamphetamine [paredrine®] hydrobromide and homatropine hydrobromide) was as follows:

OD: — 5.00 sph. ⊃ + 1.00 cyl., ax. 100 = 6/6
OS: — 0.75 sph. ⊃ + 0.50 cyl., ax. 80 = 6/6

The external examination revealed no abnormality except for a chalazion in the lateral third of the right upper lid. Exophthalmometric readings (Hertel) were 18 mm. for the right eye and 19 mm. for the left eye, at a base line of 108 mm. The visual fields, both peripheral and central, were normal bilaterally. Tonometric tension was 22 mm. Hg (Schiøtz) in each eye (dilated).

Funduscopic examination revealed no abnormality in the right eye. In the left eye the nasal portion of the retina and the optic disk were normal. In the extreme periphery (temporally and

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of the Mandible and Retina with Pronounced Hematemesis and Epistaxis, Am. J. Dis. Child. **64**:1023 (Dec.) 1942. (*d*) Brock, S., and Dyke, C.: Venous and Arteriovenous Angiomas of the Brain: Clinical and Roentgenographic Study of 8 Cases, Bull. Neurol. Inst. New York **2**:247, 1932. (*e*) Dandy, W. E.: Arteriovenous Aneurysm of the Brain, Arch. Surg. **17**:190 (Aug.) 1928. (*f*) Ehlers, H.: Aneurysma racemosum arteriovenosum retinae, Acta. ophth. **2**:374, 1924. (*g*) Elwyn, H.: Diseases of the Retina, Philadelphia, The Blakiston Company, 1946, pp. 141-172. (*h*) Feig, I.: A Case of Angioma Retinae, Brit. J. Ophth. **22**:295, 1938. (*i*) Gertz, O., cited by Ehlers,[2f] Törnquist (On an Anomaly of the Retinal Vessels [So-Called Aneurysma Cirsoides] Sometimes Combined with Symptoms from the Central Nervous System, Acta. ophth. **27**:11, 1949), and Wyburn-Mason.[1] (*j*) Gunn, R.: Direct Arteriovenous Communication on the Retina, Tr. Ophth. Soc. U. Kingdom **4**:156, 1884. (*k*) Kravitz, D., and Lloyd, R. I.: Dilated and Tortuous Retinal Vessels: Report of a Case of Congenital Arteriovenous Communication, Arch. Ophth. **14**:591 (Oct.) 1935. (*l*) Kreutz, A.: Über einem Fall von Rankenaneurysma der Arteria ophthalmica dextra, Wien. med Wchnschr. **53**:1725, 1903. (*m*) Krug, E. F., and Samuels, B.: Venous Angioma of the Retina, Optic Nerve, Chiasm and Brain: Case Report with Postmortem Observations, Arch. Ophth. **8**:871 (Dec.) 1932. (*n*) Magnus, H.: Aneurysma arteriosovenosum retinale, Arch. path. Anat. **60**:38, 1874. (*o*) Mozzetti, M.: Sulle anomalie dei vasi retinici ed in particolar modo sull'aneurisma cirsoide della retina, Boll. ocul. **18**:455, 1939. (*p*) Nicolato, A.: Angioma retinico ed angioma cerebrale. (Malformazione dei vasi cerebrali di Cushing e Bailey.), Ann. ottal. e clin. ocul. **61**:736, 1933. (*q*) Rentz, W.: Aneurysma racemosum retinale, Arch. Augenh. **95**:84, 1925. (*r*) Rienhoff, W. F., Jr.: Congenital Arteriovenous Fistula: An Embryological Study, with the Report of a Case, Bull. Johns Hopkins Hosp. **35**:271, 1924. (*s*) Ryan, E. P.: Angiomatosis Retinae, Arch. Ophth. **23**:623 (March) 1940. (*t*) Schleich, G.: Aneurysma arteriovenosum, aneurysma circumscriptum et varix (aneurysmaticus?) retinae, Mitt. ophth. Klin. Tübingen **2**:202, 1885. (*u*) Seydel: Ein Aneurysma arteriovenosum (Varix aneurysmaticus) der Netzhaut, Arch. Augenh. **38**:157, 1899. (*v*) Stokes, W. H.: Racemose Arteriovenous Aneurysm of the Retina (Aneurysma Racemosum Arteriovenosum Retinae), Arch. Ophth. **11**:956 (June) 1934. (*w*) Streeter, G. L.: The Developmental Alterations in the Vascular System of the Brain of the Human Embryo, Contrib. Embryol. **8**:7, 1918. (*x*) Törnquist, R.: On an Anomaly of the Retinal Vessels (So-Called Aneurysma Cirsoides) Sometimes Combined with Symptoms from the Central Nervous System, Acta ophth. **27**:11, 1949. (*y*) Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, pp. 978-988. (*z*) Werncke, T.: Angioma papillae nervi optici (caput medusae), Klin. Monatsbl. Augenh. **104**:434, 1940. (*a'*) Weskamp, C., and Cotlier, I.: Angioma del cerebro y de la retina con malformaciones capilares de la piel, An. argent. oftal. **1**:71, 1939. (*b'*) Weve, H.: Varix aneurysmaticus vicariens retinale, Arch. Augenh. **93**:1, 1923. (*c'*) Wilczek, M.: Eine Gefässanomalie der Netzhaut und ihr Verhältnis zur Angiomatose der Netzhaut, Zentralbl. ges. Ophth. **39**:547, 1937. (*d'*) Yates, A. G., and Paine, C. G.: A Case of Arteriovenous Aneurysm Within the Brain, Brain **53**:38, 1930.

superiorly) was a moderate-sized area of old chorioretinitis with some glial change and pigment clumping. The entire temporal portion of the retina presented a mass of dilated and tortuous vessels, which resembled a ball of worms. It was impossible to determine the character of many of the vessels, either by color or by structure. The macular area could not be made out. At least three arteriovenous communications were seen: (1) one near the temporal margin of the disk; (2) one just below the macular area, and (3) a loop anastomosis in the temporal inferior periphery. Figure 1 is a drawing of this fundus in semidiagrammatic form.

The general physical examination, including neurological tests, revealed nothing abnormal except for two café-au-lait areas of pigmentation—on the inner aspect of the right thigh and on the left buttock. No bruit could be heard over the head or the involved eye.

A roentgenogram of the chest revealed nothing unusual, and the Kahn reaction of the blood was negative.

The patient has been observed at intervals over a four-year period, with no change in the findings.

Case 2.—A white woman aged 33 was seen in the office of one of us (H. F. F.) for refraction. The family history was noncontributory except that the patient's mother had convergent strabismus.

The results of external examination were entirely normal. The visual fields, both peripheral and central, were normal. Tonometric tension was 20 mm. Hg (Schiøtz) in each eye (dilated). Refraction with cycloplegia was as follows:

O.D.: + 1.50 sph. = 6/6
O.S.: + 1.75 sph. = 6/6

Funduscopic examination showed that the right eye was normal in all respects except for the vessels on and near the disk on the nasal side. An intercommunicating vessel extended from the inferior arterial branch of the central retinal artery, on the disk, to the superior nasal vein, just off the superior nasal border of the disk. This anomalous vessel passed over a large arteriolar branch of the superior branch of the central retinal artery and assumed the characteristics of a vein as it ran toward the periphery. On careful observation, it could be seen that blood shunted back and forth in this vessel at times and that the vessel remained almost empty at other times. In every other respect the retinal vessels were normal in position and structure, except that the inferior retinal vein presented a bulbous enlargement on the disk. The left eye appeared entirely normal.

General physical examination revealed nothing abnormal. No bruit could be heard over the head or the involved eye. X-ray examination of the chest and a Kahn test of the blood were not made. Figure 2 is a semidiagrammatic drawing of the involved fundus.

Case 3.—A white girl aged 8 yr. was admitted to the contagious-disease unit of University Hospital on Oct. 6, 1939, with a history of recurrent headaches since the age of 5 yr. The headaches were often associated with vomiting, which was not projectile. About one year prior to her admission there was an acute episode of headache, abdominal cramps, and vomiting, followed by four to five days of coma, from which she recovered completely except for progressive weakness of the right arm and leg. Two weeks prior to admission there was onset of fever, urinary retention, vomiting, increasing stupor, and twitching of the left arm. The patient had had frequent profuse epistaxes from the left nostril all her life, and four to five days prior to her admission a severe nosebleed occurred from the left side. The parents stated that the patient had had a defect over the left frontal boss since birth and that at times a soft, bluish mass protruded from this area. The left pupil was dilated for one year prior to her admission. A lumbar puncture done at another hospital three days before the patient's admission revealed red blood and pus cells. A tentative diagnosis of brain tumor or brain abscess with secondary sinus thrombosis and meningitis was made. The family history, birth, developmental, and feeding histories were not remarkable.

Physical examination revealed an emaciated white girl who was stuporous and acutely ill. The temperature was 105.8 F. rectally. Over the left frontal boss was a 3-cm. linear defect from which protruded a soft, spongy mass, rising slightly above the surrounding skin and having a bluish hue. A bruit was heard over the left temple and the left orbit. The left upper lid and left lateral aspect of the nose showed a spongy tumescence. The right fundus was normal, but the left fundus showed wide, tortuous vessels. There was crusted blood in the left naris.

*Summary of Cases of Arteriovenous Aneurysm of Retina Reported in the Literature*

| Date | Author | Sex and Age | Eye | Vision | Fields | Symptoms | Associated Pathologic Condition | Funduscopic Findings |
|---|---|---|---|---|---|---|---|---|
| 1874 | Magnus [20] | M 29 | O.D. | Counting fingers | ..... | Visual loss | None reported | Direct communication between inferior temporal artery and vein; superior temporal and inferior nasal retinal vessels dilated and tortuous |
| 1884 | Gunn [21] | F 11½ | O.S. | 20/20 | ..... | Convulsions at age 1 mo.; very excitable; headache, nausea and vomiting | None reported | Communication between superior temporal artery and inferior temporal vein; several veins communicated with choroidal circulation |
| 1885 | Schleich [21] | M 8 | O.D. | Nil | ..... | Visual loss | Murmur on auscultation over affected eye | Communication between superior and inferior temporal arteries; direct arteriovenous communication in superior temporal quadrant |
| 1899 | Seydel [22] | M 18 | O.S. | 6/9 | Normal | Slight weakness of sight | None reported | Anastomosis between superior temporal artery and vein; many aneurysmal dilatations of superior temporal artery near disk |
| 1908 | Kreutz [21] | M 28 | O.D. | 0.5 | Normal | Pulsating exophthalmos | Pulsating mass in right common carotid artery; pulsation of right ear lobe | Tangle of tortuous and dilated arteries and veins; no definite communication; admixture of dark and light blood in vessels |
| 1916 | Gertz [21] | | | | | | | |
| | Case 1 | F 21 | O.S. | 5/36 | ..... | Visual loss | None reported | Inferior temporal artery dilated and tortuous and apparently communicated with inferior temporal vein |
| | Case 2 | F 37 | O.S. | 5/6 | ..... | Dimness of vision; nervousness | None reported | Some edema of retina and star figure of macula; communication between inferior temporal artery and vein in twisted vascular loop lateral to macula |
| 1923 | Weve [24a] | M 52 | O.S. | 1/4 Normal | O.D. normal; slightly constricted for color O.S.; enlarged blindspot | Visual loss | Severe nosebleeds and homolateral headache; telangiectasis of lips, conjunctiva, and cheeks | Communication between inferior nasal vein and superior nasal artery; communication between inferior temporal artery and inferior nasal vein |
| 1924 | Ehlers [25] | F 65 | O.S. | 6/6 | Normal | Mist and flashes before left eye | Bilateral ptosis | Inferior retinal artery dilated and tortuous and forming a large loop, which returned to disk; in latter part of course artery assuming venous character |
| 1925 | Rentz [26] | M 23 | O.D. | 5/35 | Normal | Visual loss | Positive Wassermann reaction | Communication between inferior temporal artery and vein and also superior temporal vein |
| 1932 | Krug and Samuels [28] | M 21 | O.D. | Nil | O.S. normal | Mental changes; defective speech; visual loss; tinnitus | Slight proptosis of right eye; angiomatous lesion of right side of face and temple; pulsation of right carotid and temporal arteries; systolic bruit over temporal region; angiomatous mass found extending from right retina along optic nerve, chiasm, and tract to midbrain and cerebellum | Great engorgement and tortuosity of veins, so that disk was almost completely obscured; arteries not enlarged where visible; no visible communication between vessels |

*Summary of Cases of Arteriovenous Aneurysm of Retina Reported in the Literature*—Continued

| Date | Author | Sex and Age | Eye | Vision | Fields | Symptoms | Associated Pathologic Condition | Funduscopic Findings |
|---|---|---|---|---|---|---|---|---|
| 1933 | Nicolato [29] | M 25 | O.S. | Counting fingers at 50 cm. | Normal | Visual loss transitory diplopia; vertigo; weakness of right side | Right hemiplegia; weakness of right lower face; proptosis of left eye; left divergence; arteriovenous aneurysm of left temporo-parietal region shown in arteriogram | Enormous increase in number and caliber of vessels; impossible to tell arteries from veins, but vessels correspond to superior and inferior temporal vessels, some vessels having disk and looped back |
| 1934 | Stokes [27] | F 10 | O.S. | 20/15 | Normal | None | None reported | Communication between superior temporal artery and inferior temporal vein, and anastomoses with choroidal circulation; another communication between branch of superior temporal vein and artery |
| 1935 | Kravitz and Lloyd [28] | F 32 | O.D. | 20/20 | Normal | None | None reported | Huge arteries and veins with much tortuosity; arteriovenous communication in inferior periphery; vessels 5 times normal size; impossible to tell arteries from veins |
| 1937 | Wiliczek [30] | F 22 | O.S. | ..... | ..... | Decreased vision | ..... | Disk normal; anastomosis in inferior temporal quadrant between macula and periphery; venous anastomosis with choroidal circulation near macular area; vessels containing arteriovenous blood |
| 1938 | Bonnet, Deschaume, and Blanc [25] | | | | | | | |
| | Case 1 | F 23 | O.S. | Nil | Temporal defect in O.D., suggesting right homonymous hemianopsia | Visual loss | Right hemiparesis; mental retardation; cirsoid aneurysm of left orbital region with pigmentation and ptosis of left upper lid; calcification left parietal region seen with x-rays | Extreme dilatation and tortuosity of retinal vessels; cirsoid aneurysm |
| | Case 2 | F 27 | O.D. | Light perception | Normal | Visual loss | Left hemiplegia; cirsoid aneurysm of right orbit with pigmentation of skin of ophthalmic division of trigeminal nerve; rarefaction in right frontal area and right sphenoid sinus greatly enlarged, as seen with x-rays | Disk pale; greatly dilated and tortuous vessels emerging from disk; cirsoid aneurysm |
| 1938 | Feig [26] | F 45 | O.D. | Moving objects | ..... | Visual loss; right divergent strabismus | Nothing reported but "nervousness"; small angioma of scalp and three small nevi on skin of abdomen | Tremendous mass of dilated vessels overlying disk, which was not visible |
| 1939 | Morzetti [20] | M 16 | O.U. | O.D.: 1/10<br>O.S.: moving objects | O.D.: Hemianopic nasal defect<br>O.S.: not obtainable | Blurred vision | Seventh-nerve paralysis on right; roentgenogram of skull showing vascular malformation of brain in occipital region | O.D.: communicating aneurysm of vessels in superior temporal quadrant<br>O.S.: communicating aneurysm of vessels in inferior temporal quadrant |
| 1939 | Weskamp and Cotlier [24] | F 17 | †O.D. | ..... | ..... | Recurrent headache; epileptic seizures | Two wine-colored areas in occipital region of scalp; vascular malformation of capillary type (biopsy); calcification at top of Rolandic region (x-rays); cavernous type of angioma of brain revealed on surgical removal of tumor from inferior pre-Rolandic region | Tumor mass, approximately 2 × 2 disk diameters located 40° from disk in temporal fundus; dilated branch of superior temporal vein penetrating and disappearing in tumor; its course traced with great difficulty; vein reappearing on opposite side of tumor with characteristics of artery; whole tumor located within two arterial branches extending from superior temporal artery; number of red spots, interpreted as miliary aneurysms, between area of entering vein and emerging artery; rest of fundus normal and media clear |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1940 | Ryan [28] | M 13 | O.S. | Counting fingers | ..... | Visual loss | None reported | Immensely dilated, tortuous, and distorted vessels covering disk |
| 1940 | Wernecke [29] | F 27 | O.D. | Light perception | ..... | Visual loss | Left hemiparesis; paralysis of right side of face, associated with lagophthalmos; right divergent strabismus | Mass of dilated vessels lying on optic disk and obscuring it; no definite arteriovenous communication |
| 1942 | Bower, Ditkowsky, Klein, and Bronstein [2c] | M 9 | O.S. | Nil | ..... | Visual loss; severe epistaxis and hematemesis | Bluish discoloration over left cheek with thrill and bruit over this area; cystic area on left side of mandible and slight enlargement of left optic canal seen with x-rays | Large number of tremendously enlarged and tortuous vessels; no definite arteriovenous communication |
| 1943 | Wyburn-Mason [1] | | | | | | | |
| | Case 1 | M 25 | O.D. | 6/9 | ..... | Headache; malaise; personality change | Subarachnoid hemorrhage; signs of vascular lesion in right side of midbrain; left hemiparesis; paresis of right inferior and internal rectus muscles | Numerous abnormal vessels; arteries could not be told from veins |
| | Case 2 | M 16 | O.D. | 6/36 | Normal | Headache; irritability; diplopia; emotional instability | Café-au-lait patch on left side of chest; signs of midbrain lesion; subarachnoid hemorrhage; paresis of right superior rectus | Superior temporal vein dilated, with three small aneurysmal dilatations; beyond this, vein passed into arteriovenous aneurysm |
| | Case 3 | F 25 | O.S. | 6/9 | ..... | Recurrent headaches; vomiting; unconsciousness; diplopia | Paralysis of left internal rectus; mental depression; systolic murmur on left side of skull | Greatly enlarged inferior temporal artery and vein communicating near periphery; several aneurysmal dilatations on artery |
| | Case 5 | F 29 | O.D. | 6/18 | ..... | Headaches and vomiting | Slight proptosis on right; bilateral ptosis (right more than left); right divergence; weakness of left side; murmur over right occipital region | Disk blurred; artery running downward from center of disk with spindle-shaped dilatation at beginning; lateral to disk, another dilated artery running to macula with small aneurysms; above disk several tortuous vessels apparently communicating with choroidal vessels; difficulty in telling arteries from veins |
| | Case 6 | M 18 | O.D. | 6/60 | ..... | Headache; blurred vision; lethargy; diplopia | Right-3d-nerve paresis; systolic murmur over entire head, especially over both eyes and right ear; weakness of left side; bilateral partial ptosis, on right more than left | Vessels engorged and tortuous, especially near disk; arteries and veins of same caliber and greatly increased in size; direct communication between superior temporal artery and vein; direct communication between superior nasal vessels; below disk large vessel communicating with choroidal circulation |
| | Case 7 | M 32 | O.S. | 6/6 | Right homonymous hemianopsia | Petit mal attacks; patient depressed and asocial; headaches; progressive deafness in right ear with constant pumping noise | Enormous hydrocephalus; vascular nevus of left side of forehead; several large pigmented nevi over body; right divergent strabismus; loss of conjugate upward voluntary movement; weakness of left leg | Direct communication of superior temporal artery and vein at periphery; artery and vein both enlarged and number of small aneurysms on artery near disk |
| 1949 | Törnquist [28] | F 31 | O.S. | Normal | Normal | Severe headache; intermittent weakness of right arm and leg | None reported | Several communications between inferior temporal artery and vein in inferior temporal periphery |
| 1951 | Bíró [2a] | F 9 | O.D. | 5/10 | Normal | Slightly defective vision | None reported | Network of dilated vessels, 10-15 times original diameter, covering disk and macula; mass of vessels protruded 4 D. at disk but flattened out toward periphery; anastomoses impossible to distinguish; vessels uniform in color |

Fig. 1.—Semidiagrammatic drawing of the fundus in Case 1.

Fig. 2.—Semidiagrammatic drawing of the fundus in Case 2.

Brudzinski and Kernig signs were elicited. The right arm and leg showed marked loss of tone, with general atrophy of the muscles of the forearm and hand. The Babinski sign was elicited on the right, and the reflexes were hypoactive throughout. The blood pressure was 114/76. Results of the general physical condition were otherwise normal.

*Laboratory Findings.*—The hemoglobin concentration was 56%. The white blood cell count was 17,600. The Kahn reaction of the blood was normal. The urine was normal. Lumbar puncture revealed a pressure of 200 mm. of water, and the fluid contained hemolyzed red and white blood cells. Culture of the spinal fluid yielded no growth.

*Course in Hospital.*—The patient was transferred to the neurosurgical service, where a second lumbar puncture revealed an initial pressure of 190 mm. of water. This was reduced to 90 mm. of water by removal of 20 cc. of spinal fluid. The total cell count was 1,750 of which 790 were white blood cells (85% polymorphonuclear leucocytes). A roentgenogram of the skull showed a slight increase in volume of the left orbit and localized rarefaction, extending in from the midportion of the inner table of the left frontal bone. The findings on ophthalmologic examination were as follows: Visual acuity could not be determined. The eyes were straight, and the pupil measured 2 mm. in the right eye and 4 mm. in the left eye. A slight proptosis of the left eye was present. Findings on external examination were otherwise normal. The fundus of the right eye was entirely normal. Funduscopic examination of the left eye revealed that the media were clear. The region of the disk contained an enormous number of dilated vessels, both arteries and veins, which were almost impossible to differentiate as to type. The disk margins were obscured by these vessels, which filled almost the entire posterior third of the vitreous. The macular area was also obscured. The periphery of the retina was relatively normal.

A carotid arteriogram on the left showed a racemose type of hemangioma medial to the inferior portion of the motor area. At the time this was taken the left internal carotid artery was palpated and did not appear abnormal. The left common carotid and external carotid arteries were ligated. Three weeks later an osteoplastic craniotomy was performed on the left side. Upon exposure of the brain, the middle cerebral artery was observed to be extremely dilated, and silver clips were placed along it, reducing the lumen to approximately one-fifth or one-sixth its previously distended size. Admixture of venous and arterial blood could be seen in this vessel. From the circle of Willis several tortuous vessels were noted to accompany the left optic nerve as it entered the left optic foramen. Two of these were clipped and severed. The patient was discharged from the hospital on Nov. 26 in a fairly satisfactory condition.

*Subsequent Course.*—In spite of several attempts at follow-up examination, the patient was not seen again until Dec. 16, 1946, at the age of 15. For two months prior to this admission (second) she had been bedridden with severe headaches. At this time it was found that there was paralysis of the right arm and leg. Aphasia was present, but she was able to speak two or three syllables. After a general physical examination was performed, the patient was discharged from the hospital, since futher treatment would have been of no benefit. The case was regarded as hopeless. Unfortunately, an ocular examination was not done. The patient died at home on June 21, 1950. Permission for autopsy was not obtained.

## COMMENT

Cerebral and ocular vascular malformations are of three types: (1) telangiectases (capillary formations); (2) venous angiomas, and (3) arteriovenous aneurysms (cirsoid, racemose, serpentine, plexiform, and cavernous angiomas). These vascular malformations are separate and distinct from true vascular neoplasms, such as the hemangioblastomas. They should be distinguished also from purely arterial malformations, such as congenital aneurysm of the circle of Willis, or cavernous sinus-carotid artery fistula, which is usually of traumatic origin. Arteriovenous aneurysms are divided into three types: (1) a direct end-to-end communication between artery and vein; (2) a network of vessels, the so-called angioma, situated between an artery and one or several veins, and (3) an anomalous vessel of congenital origin establishing a communication between an artery and a vein. In all types

a capillary bed is lacking between the artery and the vein. Thus, arterial blood passes directly into the venous system. In many of the reported cases the conglomeration of dilated, tortuous, and dark-colored vessels, which replace the retinal vascular tree, points to the existence of an arteriovenous communication, even though such a communication cannot always be visualized. From the clinical standpoint it often cannot be decided whether the vascular malformation is of a congenital arteriovenous type or whether it originally was a venous angioma which had undergone a process of arterialization. In an arteriovenous aneurysm the blood passes from the arterial to the venous side in such quantities that growth and enlargement of the supplying artery usually occur. This is not true of the venous angioma, but often the types of vascular malformation are not clear-cut. What appears to be a purely venous anomaly may occasionally acquire an arterial component with the passage of time. A venous angioma consists of a simple varix and single or multiple tortuous veins. A racemose angioma consists of a mass of pulsating vessels and is correctly considered an arteriovenous aneurysm.

The embryonic development of the cerebral and retinal vasculature affords a basis for the understanding of these anomalies. Streeter divided the development of the blood vessels of the brain into five arbitrary periods: (1) angioblastic period, in which the primordial vascular system of channels, neither arteries nor veins, is established; (2) resolution of the primordial system into arteries, veins, and capillaries; (3) cleavage of the vascular system of the head into the external, dural, and cerebral layers; (4) adjustments of the vessels to growth and change in form of the surrounding structures; (5) histological differentiation of the walls of the vessels into adult arteries, veins, and various types of sinuses, which takes place after the 50-mm. stage and the third month. Aberration of this differentiation into capillaries, arteries, and veins arising from the primordial blood-containing vessels results in the various types of vascular malformations previously noted.

Rienhoff stated that injection of pig embryos with India ink proved that development of the blood-vascular system is from a uniform capillary network rich in anastomoses, offering ample opportunity for the formation of an arteriovenous fistula. After many unsuccessful attempts, persistence of a communication between well-developed arterial and venous trunks in a chick embryo was produced by irritation of endothelial cells, forming a true arteriovenous fistula.

Wyburn-Mason [1] has established the syndrome of arteriovenous aneurysm of the midbrain and retina, associated with facial nevi and mental changes. Essentially the same syndrome was described by Bonnet, Dechaume, and Blanc.[2b] Bower, Ditkowsky, Klein, and Bronstein [2c] described a case of arteriovenous angioma (aneurysm) of the mandible and retina with pronounced hematemesis and epistaxis. Vascular nevi of the skin have been described in several cases. If ocular involvement is present, these nevi are always located on the same side as, and in the region of distribution of, the trigeminal nerve. Pigmented nevi have been described in other locations in several cases.

In some of the reported cases of vascular malformations of the brain, dilated and tortuous retinal vessels have been described. These may have been arteriovenous aneurysms of the retina; but since they were not so regarded by the authors, they were not included in the summary of cases from the literature. The cases reported by Gertz [21] may not have been arteriovenous in nature; he considered that the condition resembled closely von Hippel's disease. In a case described by

Weve [2b'] the picture was one of congenital arteriovenous aneurysm of the retina but was interpreted by him as collateral vicarious anastomoses following vascular obstruction. Werncke's [2z] case is included in the summary of cases from the literature, since it could actually represent an arteriovenous aneurysm of the retina. The associated hemiparesis, facial palsy, and strabismus suggest a vascular malformation of the brain. A case presented by Ryan [2s] is also included in the summary, since the anomaly closely resembled the disease under discussion, and the author considered it a congenital abnormality of the retinal vessels. The lesion in the case of Weskamp and Cotlier [2a'] simulated angiomatosis retinae but was probably arteriovenous aneurysm, since the surgical specimen revealed a cavernous type of angioma of the brain.

Some authors (Törnquist,[2x] Wilczek [2c']) have stated that in many of the reported cases there are resemblances between retinal racemose aneurysm and angiomatosis retinae. They believe that the former condition can pass over into the latter, even though definite supportive evidence is lacking.

When there is associated intracranial involvement, roentgenograms of the skull may reveal calcified areas, appearing as characteristic circles or whorls. In the absence of intracranial calcification there may exist marked dilatation and tortuosity of grooves in the bones of the skull, but in many cases roentgenograms of the skull may show no lesion. The retinal arteriovenous aneurysms, being nonprogressive, do not require treatment. If the aneurysm is occasionally progressive, and if situated far enough in the periphery, treatment by irradiation or diathermy may be considered. In the presence of an associated intracranial lesion the attention of the neurosurgeon is required. The advent of cerebral angiography has aided greatly in the diagnosis of these intracranial vascular malformations. The possibility of concurrent intracranial vascular abnormality, almost invariably located on the same side as the ocular signs, must again be emphasized.

The first two cases reported in this paper are considered to be instances of involvement of the retinal vascular system alone, without involvement of blood vessels of any other location. It is acknowledged that the examination in each case was incomplete, since roentgenograms of the skull, electroencephalograms, etc., were not obtained. The absence of symptoms and the completely normal physical findings would indicate that intracranial or other involvement was not present. Case 3 of this report is regarded as typical of the syndrome described by Wyburn-Mason [1] and others. It is regretted that it was not possible to obtain a more complete ophthalmologic study and a photograph or drawing of the fundus.

### OPHTHALMIC DIFFERENTIAL DIAGNOSIS

Congenital tortuosity of the retinal vessels may be encountered frequently in eyes with hypermetropia of high degree and occasionally in normal eyes. Vascular intercommunications, as well as tortuosities and varicosities of the retinal veins, may result from prolonged pathologic vascular stasis occurring with arteriosclerosis, venous thrombosis, arterial emboli, or chronic glaucoma, or after retinal hemorrhage. Peripheral anastomoses may occur between the retinal and the choroidal vessels after chorioretinitis. It is questionable whether trauma can produce retinal arteriovenous communication, but since this factor has not been definitely excluded, it may be mentioned. Cyanosis retinae, with greatly enlarged and tortuous vessels, can simulate this picture, but there are no arteriovenous communications, and

general cyanosis with cardiac disease is usually present. Polycythaemia vera may also be mentioned, and its presence can be demonstrated by careful study of the blood.

Pulsating exophthalmos can effect greatly enlarged and tortuous retinal vessels, but there are no retinal vascular intercommunications. A bruit is usually demonstrable on auscultation, and compression of the carotid artery will cause the orbital pulsation to decrease. The Sturge-Weber syndrome must be considered in any case. The major features of meningeal calcifications, naevus flammeus, glaucoma, and, predominantly, choroidal changes are helpful differential aids. Angiomatosis retinae (von Hippel's disease) is likely to be confused with arteriovenous aneurysm. In fact, the first case of the former was erroneously published by Fuchs in 1882 under the name of arteriovenous aneurysm. Helpful differentiating features are the presence of a hemangioblastoma in the periphery, with accompanying exudate, and slow progression of the disease.

Congenital macular "colobomas" may be associated with abnormal vessels and anastomoses between the retinal and the choroidal circulation. Congenital aneurysms of the retinal arteries are extremely rare, and their relationship to arteriovenous aneurysms is not clear. They are probably more clearly related to congenital aneurysms of the circle of Willis.

## SUMMARY

Congenital arteriovenous aneurysm of the retina may exist as an isolated entity or be associated with arteriovenous aneurysm or vascular malformation in other locations, especially the brain.

Cases of this anomaly in the available literature are summarized in tabular form.

Three cases of congenital arteriovenous aneurysm of the retina are presented. Two of these are considered to show retinal involvement alone, without abnormality of vessels elsewhere. The third case is regarded as typical of the syndrome described by Wyburn-Mason.

A brief description of the cerebral and ocular vascular malformations and their embryologic basis is given.

An ophthalmologic differential diagnosis is presented.

Miss Janet McLaughlin, medical illustrator, University Hospital, prepared the fundus drawings in Cases 1 and 2 reported in this paper.

# PREGNENOLONE THERAPY IN UVEITIS

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THE DRAMATIC suppression of certain inflammatory reactions by cortisone and corticotropin (ACTH) is now well known. In the search for effective substitutes for these drugs, numerous other substances have been subjected to clinical trial by various investigators. One of these is $\Delta^5$-pregnenolone ($\Delta^5$-pregnen-3-$\beta$-ol 20-one), usually referred to as pregnenolone, which is chemically related to the adrenal corticosteroids. Some published reports [1] claim good therapeutic action in rheumatoid arthritis with this drug. This suggested the possibility that pregnenolone might be a readily available, easily administered, and nontoxic medication for uveitis, which usually responds well to cortisone and corticotropin.

Pregnenolone was given to 10 patients with various forms of uveal inflammation. This series consisted of one case each of the following diseases: recurrent exudative chorioretinitis, acute granulomatous uveitis with secondary glaucoma, malignant cyclitis following retinal detachment, chorioretinitis juxtapapillaris, granulomatous iridocyclitis associated with parotitis, recurrent nodular iritis, recurrent plastic iritis with secondary glaucoma, post-traumatic cyclitis, and Harada's disease with bilateral retinal detachment (two cases). All these patients had undergone diagnostic investigations, which included physical and dental examination, inspection of the nose and throat, x-ray studies of the chest, and Mantoux testing. No specific cause of the ocular condition was proved in any of the cases. Pregnenolone was administered at various stages in the course of these diseases. Some of the patients had previously received nonspecific foreign-protein therapy, antibiotic treatment, and chemotherapy, with little or no effect. At the time of administration of pregnenolone, the inflammation was in an active phase in all cases, and all other medication except use of atropine-sulfate drops had been stopped. Pregnenolone was given for periods of one to two weeks in amounts reported as effective in rheumatoid arthritis. Eight patients received pregnenolone orally, 100 mg three times a day, and two patients received pregnenolone intramuscularly, 100 mg. once a day.

In nine of the patients the disease showed no change or became worse during treatment with pregnenolone. The eye with the detached retina and severe cyclitis

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From the ophthalmological service of Dr. R. Townley Paton, Manhattan Eye, Ear and Throat Hospital, New York.

1. Freeman, H.; Pincus, G.; Johnson, C.; Bachrach, S.; McCabe, G., and MacGilpin, H.: Therapeutic Efficacy of $\Delta^5$-Pregnenolone in Rheumatoid Arthritis: Preliminary Observations, J. A. M. A. **142**:1124-1128 (April 15) 1950. Davison, R.; Koets, P.; Snow, W., and Gabrielson, L.: Effects of $\Delta^5$-Pregnenolone in Rheumatoid Arthritis, Arch. Int. Med. **85**:365-388 (March) 1950.

was enucleated to relieve pain shortly after a two-week course of treatment with pregnenolone. After the patient with recurrent plastic iritis and secondary glaucoma had been given pregnenolone orally for one week, without benefit, treatment was changed to instillation of cortisone eye drops every two hours in a concentration of 4 mg. per cubic centimeter. Within three days of such local cortisone therapy, there was pronounced symptomatic and visual improvement, and at the end of one week the intraocular pressure, which had ranged from 40 to 46 mm. Hg (Schiøtz), dropped to 23 mm. Hg, while the iritis appeared to have subsided. In a 15-year-old girl with Harada's disease of four-months' duration, the retinal detachments seemed to be gradually receding in both eyes and the media clearing before pregnenolone therapy was begun. The slow improvement continued during and after two weeks of ingestion of pregnenolone, without apparent alteration in the course of the disease. Only one patient showed any distinct improvement while receiving pregnenolone. This was a man aged 30 with chorioretinitis juxtapapillaris in one eye, who had noted blurring of vision for 10 days. By the sixth day of pregnenolone therapy a decrease in the area of retinal edema was seen, and by the 10th day the area of retinal edema was one-half its original diameter. At this time pregnenolone was discontinued, and the retina continued to clear at the same rate over the next two months. However, the loss of visual field, consisting of an incomplete sector defect, remained permanent.

None of the 10 patients who were given pregnenolone displayed any toxic effects as a result of the drug. The lack of any effect, beneficial or toxic, in nearly all these cases of inflammatory ocular disease is in accord with those investigators [2] who report absence of favorable results with the use of pregnenolone in rheumatoid arthritis. Even in the one case in this series in which the patient displayed distinct improvement during pregnenolone therapy, there is some doubt as to the efficacy of the drug. The failure of the patient to relapse on withdrawal of pregnenolone five days after initial regression of the inflammation indicates that the improvement may have been coincidental.

SUMMARY

Ten patients with various types of active uveitis were given a trial of $\Delta^5$-pregnenolone therapy. Nine of the 10 patients failed to show any change as a result of this treatment.

Pregnenolone was supplied by Ayerst, McKenna & Harrison, Ltd.

2. Polley, H. F., and Mason, H. L.: Rheumatoid Arthritis: Effects of Certain Steroids Other Than Cortisone and of Some Adrenal Cortex Extracts, J. A. M. A. **143**: 1474-1481 (Aug. 26) 1950. Guest, C. M.; Kammerer, W. H.; Cecil, R. L., and Berson, S. A.: Epinephrine, Pregnenolone and Testosterone in the Treatment of Rheumatoid Arthritis, ibid. **143**: 338-344 (May 27) 1950. Smith, R. T.: Testosterone, Pregnenolone and Irradiated Ergosterol in Treatment of Rheumatoid Arthritis, Philadelphia Med. **45**: 1201-1202 (April) 1950.

# OCULAR TUMORS

## A Study of Incidence of the Various Types and Their Mortality Rates

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THE ACCOMPANYING tables represent a statistical analysis of 170 consecutive cases of ocular tumors as these have appeared over a period of 10 years. They represent the cases from the Wills Hospital, the Graduate Hospital of the University of Pennsylvania, and Jeanes Hospital—private, ward, and clinic patients, whom I have seen and whose surgical or x-ray treatment I have carried out or

TABLE 1.—*Incidence and Mortality of Malignant Melanomas of the Eye*

| | No. of Cases | Deaths |
|---|---|---|
| Malignant melanomas | 33 (20%*) | 5 (16%†) |
| Iris and ciliary body | 4 | 0 |
| Other intraocular melanomas | 17 | 3 |
| Total | 21 (68%†) | |
| Extraocular | 11 (32%†) | 2 |
| Nonpigmented melanoma of lid, recurrent | 1 | |

* Percentage of all ocular tumors.
† Percentage of melanomas.

TABLE 2.—*Neurogenic Tumors of the Eye*

| | No. of Cases |
|---|---|
| Neurofibroma of orbit and/or lids (neurofibroma molluscum and schwannoma) | 10 |
| Neurofibroma of orbit, lids, and region of zygoma, undergoing sarcomatous changes 7 yr. later | 1 |
| Plexiform neuroma of optic nerve | 1 |
| Neuroma of optic nerve (neurogenic fibroma) | 3 |
| Meningioma of sheath of optic nerve | 1 |
| Retinoblastoma | |
| Bilateral | 2 |
| Unilateral (1 death) | 7 |
| % of all ocular malignant tumors | 5.6 |

directed. The histopathologic study of these tumors is not included. The pathologists at the three institutions mentioned made the diagnoses in all instances, and in some cases sought confirmation by consultation with other pathologists.

Tumors not purely ocular have not been included, e. g., meningioma of the sphenoidal ridge and/or of the frontal fossa, malignant growths of the optic chiasm, and the various types of primary and metastatic intracranial malignant neoplasms.

The mortality rate for some of these tumors will certainly change over the years to come. This change can only be one of increasing mortality; therefore, the incidence given is probably the most optimistic possible.

Presented at the Third Annual Clinical Conference, the Wills Hospital, March 16, 1951.

TABLE 3.—*Ocular Sarcomas, Including Tumors of Lymphatic System and Blood Vessels*

| | | No. of Cases | % of Ocular Tumors |
|---|---|---|---|
| Tumors of lymph cells | | 11 | 6.1 |
| Lymphosarcoma | 8 | | |
| Classic reticulum-cell type | 2 | | |
| Follicular lymphoma | 1 | | |
| Lymphoblastoma | 2 | | |
| Hemangioma (angioma) | | 10 | 6.0 |
| Lids (all infants) | 5 | | |
| Lid, pigmented, later diagnosed as basal-cell carcinoma; complete recovery | 1 | | |
| Intraorbital | 4 | | |
| Sarcoma | | 25 | 15.0 |
| Giant-cell sarcoma | 1 | | |
| Osteogenic | 2 (1 known death) | | |
| Intraocular | | | |
| Primary | 1 | | |
| Metastatic | 2 (both deaths) | | |
| Retrobulbar, primary | 16 | | |
| Mixed and spindle-cell, with 3 deaths, 2 in children; extension into orbit from sinus | 1 | | |
| Conjunctival, subepithelial, and scleral | 3 | | |
| Following trauma (death) | 1 | | |

TABLE 4.—*Miscellaneous Ocular Tumors*

| | No. of Cases | Deaths |
|---|---|---|
| Hypernephroma (neuroblastoma) (One infant; one slightly older child) | 2 | 2 |
| Osteoma of orbit | 1 | |
| Lipoma of orbit * | 1 | |
| Ewing's tumor † | 2 | 2 |
| Mixed-cell tumor of lacrimal gland | 3 | 2 ‡ |
| Rhabdomyoma of orbit § | 1 | |
| | 1 | |

* Relatively frequent cases of prolapse of orbital fat at external canthal angle are not included.

† More properly called Ewing's syndrome. For an interesting résumé of this tumor, see Willis, R. A.: Pathology of Tumours, St. Louis, C. V. Mosby Company, 1948, p. 687.

‡ In the third case (patient still alive), there is a difference of opinion as to the histology of the tissue.

§ Death occurred later from adenocarcinoma of the breast. This is one of two cases of double malignant neoplasm. The muscle tumor started in the inferior rectus muscle.

TABLE 5.—*Epithelial-Cell Tumors of the Eye*

| | No. of Cases | Deaths |
|---|---|---|
| Adenocarcinoma, primary | 9 | 5 |
| Lid | 2 | 2 |
| Lacrimal gland (not mixed cell type) | 2 | 1 |
| Conjunctival, at limbus | 2 | 1 |
| Tarsus * | 3 | 1 |
| Adenocarcinoma, metastatic | 9 | 6 |
| From maxillary sinus | 2 | 1 |
| From breast, intraocular | 1 | 1 |
| From lung, intraocular | 1 | 1 |
| From prostate, intraocular | 1 | 1 |
| Orbitoethmoidal | 2 | 1 |
| From nose, by extension | 1 | |
| From maxillary gland (patient refused operation) | 1 | 1 |
| Carcinoma of orbit, primary | 1 | |
| Carcinoma of lacrimal sac, primary | 5 | 1 |
| Basal and squamous-cell carcinoma † | 35 | 1 |
| Total | 60 (37% ‡) | |

* One was metastatic to cervical and submaxillary glands; one, metastatic to lip, with extension to nose and to malar bone (patient died).

† Cases of epithelial-cell tumors of the lid, lid margin, conjunctiva, and canthal angles are included here; recurrence in 4 cases. One patient had an earlier malignant growth of the ovary, with surgical recovery.

‡ Percentage of all ocular tumors.

The malignant melanomas are presented in Table 1. A comment here regarding the mortality of extraocular malignant melanomas is relevant. The percentage of mortality of these tumors is not a true one. It is known, however, that recurrence of these melanomas is frequently delayed for many years.

Tumors of the nervous system are presented in Table 2. With regard to the retinoblastoma, I am not impressed with the necessity of a transfrontal exploratory craniotomy, even when a section of the optic nerve shows tumor cells within the nerve. In two instances massive x-ray therapy was wholly successful.

TABLE 6.—*Incidence of Major Types of Malignant Tumors of the Eye*

| Type | Incidence of Tumor | | Mortality | |
|---|---|---|---|---|
| | | | No. | % of Tumor Type |
| Melanoma | | 20%— | 5 | 16 |
| Neurogenic | | 15%— | 1 (retinoblastoma) | |
| Sarcoma | | 27%+ | 12 | 41 |
| Lymph-cell type | 6+ | | | |
| Angioma | 6+ | | | |
| All others | 15+ | | | |
| Miscellaneous tumors | | 2%— | | |
| Epithelial-cell tumors | | 37%+ | | |
| Adenocarcinoma | | | | |
| Primary | 15 | | 5 | 55 |
| Metastatic | 15 | | 6 | 66 |
| All other types | 70 | | 6 | 14 * |

* Percentage of mortality for carcinoma.

The sarcomas are presented in Table 3; miscellaneous tumors, in Table 4, and epithelial tumors, in Table 5. Table 6 is a recapitulation of the percentages of major tumor types and gives the mortality rates as they are now known.

At the present time the only certain conclusion one can draw from this analysis is that patients with sarcoma die early in life, and early in the course of the disease, and that adenocarcinoma is the most malignant of all the epithelial-cell tumors of the eye.

1930 Chestnut St.

# RELIEF OF SENILE ENTROPION

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SENILE entropion is a common and troublesome clinical entity. It is as troublesome to the ophthalmologist as to the patient, because minor measures are usually ineffective and yet the clinical manifestations frequently do not seem severe enough to the patient to warrant major surgical intervention. Unfortunately, only operation can effect a permanent cure, though even this is not always certain.

Most textbooks define senile entropion as a form of spastic entropion of the lower lid, or, conversely, the commonest form of spastic entropion is described as occurring in the lower lid of older people. It is usually attributed to a spasm of the orbicularis brought on by ocular irritation, either inflammatory or traumatic.

Over the years, many procedures have been suggested for the correction of this condition. However, the armamentarium of remedies offered is larger than it is effective. The commonest of these methods may be summarized as follows:

1. Collodion and adhesive have been applied to pull the lid down and away from the globe.[1] Except in the most transient cases, this method is largely useless.

2. Sutures have been employed as suggested by Gaillard,[2] Arlt,[3] Snellen,[4] Stellwag,[5] and many others. The very multiplicity of suture correctives offered mirrors their ineffectiveness, and this method is gradually fading into deserved oblivion.

3. Cantholysis[6] has occasionally been recommended but has, fortunately, not become popular.

4. Injection of alcohol[7] is uncertain or temporary in action.

5. Excision of strips of skin and/or muscle[8] of all shapes and sizes does not offer a permanent cure of senile entropion, and repetition causes lagophthalmos.

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From the Eye Service, Goldwater Memorial Hospital.

1. (*a*) Beard, C. H.: Ophthalmic Surgery, Ed. 2, Philadelphia, P. Blakiston's Son & Co., 1914, p. 253. (*b*) Wiener, M., and Alvis, B. Y.: Surgery of the Eye, Philadelphia, W. B. Saunders Company, 1939, p. 228.

2. Gaillard, A.: Bull. Soc. Med., Poitiers, 1844, cited by Beard,[1a] p. 255.

3. Arlt, C. F.: Die Krankheiten des Auges, Vol. 3, 1856, p. 368.

4. Snellen, H.: Cong. internat. ophth., Paris, 1863, p. 403.

5. Stellwag, C., cited by Beard,[1a] p. 256.

6. Pochisov, H.: Operation for Spastic Entropion, Sovet. vestnik oftal. **6**:131, 1935.

7. Duverger and Velter: Thérapeutique chirurgicale ophthalmologique, Paris, Masson & Cie., 1926, p. 93.

8. von Graefe, A., cited by Fuchs, E.: Text-Book of Ophthalmology, Ed. 5, Philadelphia,

6. The Ziegler puncture [9] has always been more effective in correction of ectropion than of entropion, and, while this procedure is useful in the milder cases of entropion, it is rarely permanent. Here, too, repetition causes lagophthalmos.[10]

7. I have seen tarsorrhaphy misused to "correct" senile entropion. This seems to be a method of resignation, as though one were to say, "It can't be cured; so let's sew the lids together." Fortunately, this method is rarely used.

8. Numerous technics for the horizontal section and resection of the tarsus, after the pattern of the Streatfield-Snellen [11] procedure, have been tried for spastic entropion. These are far more useful for the cicatricial type and are contraindicated in cases of senile entropion.

9. Wheeler's [10] transplantation of orbicularis strips is the best method to date. However, even with this procedure there are recurrences, as will be shown later. Meek's [12] modification of this operation does not improve the procedure materially.

It is fair to conclude that the surgical correction of senile entropion has not been completely successful to date and that a reevaluation of the problem seems to be in order.

That spastic entropin exists is, of course, obvious. Acute forms of this clinical entity are seen in cases of ocular inflammation, following long-continued patching, surgical procedures, and other types of trauma. They are seen in young and old persons alike and are accompanied by blepharospasm, photophobia, and lacrimation. This type of entropion is usually amenable to conservative treatment, such as application of adhesive strips or collodion, and disappears with the subsidence of the causative factor.

However, in senile entropion the clinical picture is different. Often there is no history of previous inflammation or trauma. Usually, whatever irritation is present seems to be the result of the entropion, i. e., of the lashes rubbing against conjunctiva and cornea, and not the cause. Frequently, as a matter of fact, the eye is white and quiet in a case of entropion which has persisted for years. Hence, since senile entropion is a chronic condition involving the lower lid only, it is difficult to explain it on the basis of orbicularis spasm alone, unless one postulates a long-standing, powerful, localized muscular spasm confined to the marginal fibers of the orbicularis (the muscle of Riolan) of the lower lid only. Such remarkable selectivity in a muscle spasm, presumably initiated by a persistent general ocular irritant, is hard to conceive. Obviously, there must be other factors to explain the mechanics of senile entropion.

As Wolff [13] points out, the tarsus normally lies snugly against the globe, where it is held in place by the palpebral ligaments, whose attachment is well behind the

9. Ziegler, S. L.: Galvanocautery Puncture in Ectropion and Entropion, J. A. M. A. **53**:183 (July 17) 1909.

10. Wheeler, J. M.: Collected Papers, New York, Columbia University Press, 1939, p. 412.

11. Weeks, W. W.: Surgery of the Eye, New York, School of Ophthalmology and Otolaryngology, 1937, p. 16.

12. Meek, R. E., cited by Spaeth, E. B.: Principles and Practice of Ophthalmic Surgery, Ed. 3, Philadelphia, Lea & Febiger, 1944, p. 446.

13. Wolff, E.: The Anatomy of the Eye and Orbit, Philadelphia, P. Blakiston's Son & Co., Inc., 1933, p. 89.

anterior plane of the globe. Furthermore, Adler [14] states that the muscle of Riolan is more developed in the lower lid than in the upper and helps to keep the free border against the globe. The lower tarsal border is held in place by the tarso-orbital fascia and a fibrous slip from the inferior rectus, which assists in keeping the attached border in contact with the globe.

However, the aging process, with its absorption of orbital fat and general relaxation of tissues, causes a derangement of this normal mechanism. Owing to reduction of orbital contents, the eye becomes relatively enophthalmic. The loosening of muscle and skin tissues of the lower lid reduces the pressure on the attached tarsal border, and its firm contact with the globe is lost. Hence, when the muscle of Riolan contracts, as in eye closure, the lowest tarsal border swings forward and the taut upper border, deprived of adequate support by an enophthalmic globe, tends to turn in, and a senile entropion is born. Adler [14] puts it succinctly as follows:

> Spastic entropion is . . . favored when the forces which keep the tarsus in its natural position are diminished; that is, when the tarsus itself is small or poorly developed, when the supporting structures are thin and atrophic, or when the skin of the lid is very soft and easily put out of position.

Fuchs [15] has stated:

> Entropion spasticum develops mainly in elderly people with flabby lids, and its production is favored by deep placing, diminution in size, or absence of the eyeball.

It would seem, therefore, that senile entropion is due not so much to "spasm" as to the degenerative processes of old age, which favor its occurrence. It is only after prolonged corneal irritation that the "spastic" element becomes superimposed. This concept does not require an active etiologic agent and would seem to be more compatible with the clinical facts as they exist. These are:

1. The occurrence of the condition in the lower lids of elderly people only.

2. The usual absence of any history of inflammation or irritation prior to the onset of the entropion.

3. The frequently normal appearance of the involved eye. Often, entropion is detected when the patient is seen for some other ocular complaint, as may be noted from the case reports below.

4. When the lid is pulled down manually, it frequently stays in normal position until the eye is closed or until the lids are squeezed together.

5. Any procedure which tautens the skin of the lid cures the entropion, at least temporarily. However, when the skin becomes stretched again, the condition recurs.

If there is any validity to this concept, then the methods of correction hitherto used require revision. Weakening the orbicularis by cantholysis or injection of alcohol, narrowing the lid by excision of horizontal strips of skin and muscle, and attempting to evert the lid and pulling it down by means of cautery, sutures, or strips of skin or muscle do not seem to be the logical methods of attack. It would

14. Adler, F. H.: Gifford's Textbook of Ophthalmology, Ed. 4, Philadelphia, W. B. Saunders Company, 1947, p. 159.

15. Fuchs, E.: Text-Book of Ophthalmology, Ed. 5, Philadelphia, J. B. Lippincott Company, 1917, p. 678.

seem to be more to the point to strengthen the lid vertically by tautening the lower border of the tarsus and by shortening the horizontal expanse of the orbicularis and skin. In other words, the lid tissues should be strengthened not by horizontal, but by vertical, resection of the involved tissues. To attain this end, the following procedure was adopted.

### TECHNIQUE OF OPERATION (FIG. 1)

The external half of the lid is split into skin-muscle and tarsoconjunctiva layers to a depth of 10 mm. At the medial end of the incision a triangle of the tarsoconjunctival tissue, apex

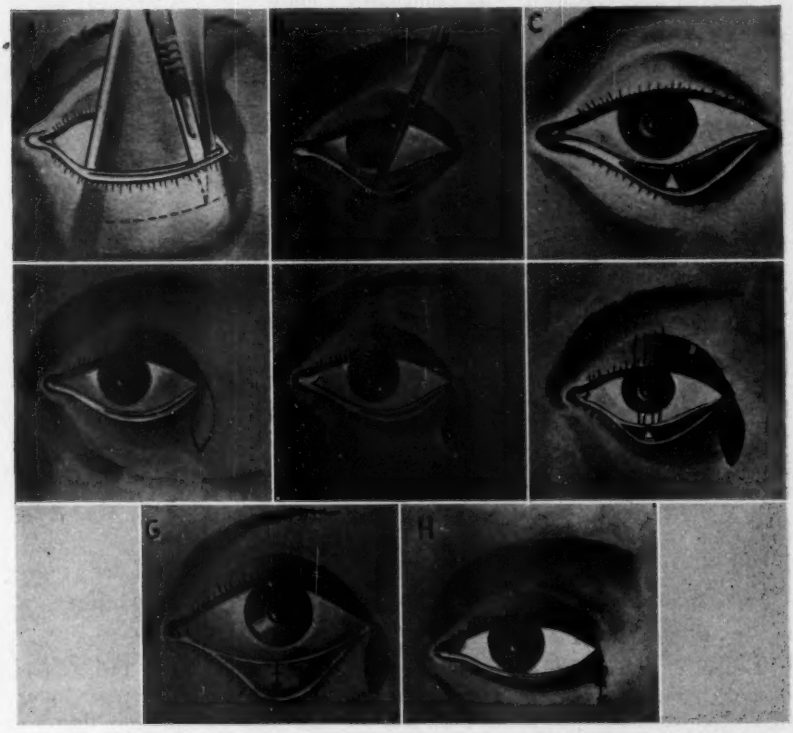


Fig. 1.—(*A*) The external half of the lid is split to a depth of 10 mm. (*B*) A triangle, apex upward, is marked out on the tarsus. The base at the attached border measures 5 mm. (*C*) The tarsal triangle is resected. (*D*) A spindle, measuring 15 mm. vertically and 8 to 10 mm. horizontally, is marked out just below the external canthus. (*E*) The included skin and muscle are resected. (*F*) Two 4-0 braided black-silk sutures are inserted in the tarsal wound. (*G*) The sutures are tied on the conjunctival surface. (*H*) The skin wound is closed with several 5-0 braided black-silk sutures.

upward, is resected. The base should not measure more than 5 mm. and is formed by the attached tarsal border. Just below the outer canthus of the lid a spindle of skin and muscle, measuring 15 mm. vertically and 8 to 10 mm. at its widest horizontal point, is resected. The upper pole of the spindle is at the lid margin. The tarsal incision is closed with two or three 4-0 braided black-silk sutures tied on the conjunctival side. The skin incision is also closed with

several interrupted 5-0 braided black-silk sutures. If one desires, one may insert one or two through-and-through sutures at the marginal split to assure proper coaptation.

A firm supportive dressing is applied. The eye is dressed in 48 hours, and the marginal sutures are removed. The eye is inspected daily thereafter, and the skin sutures are removed on the fifth day. The tarsal sutures are removed on the 10th day.

## REPORT OF CASES

The technique described above was used on 14 lids, of 10 patients. In a case of bilateral involvement (Case 5) mild ectropion of the right lower lid developed immediately after operation. This complication righted itself spontaneously within 10 days. It was believed due to the excision of too large a tarsal triangle—7 mm. at the base. On no account should the base of the excised triangle measure more than 5 mm.

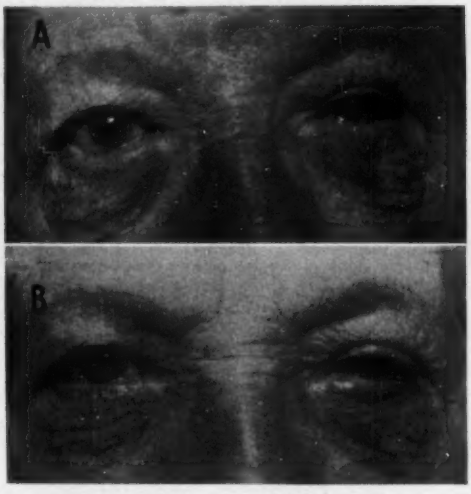


Fig. 2 (Case 1).—*A*, bilateral senile entropion; *B*, 20 months after operation on the left lower lid and four weeks after operation on the right lower lid.

Length of observation has varied from 20 months (Case 1) to two months (Case 8). Five of the 14 eyes have been under observation a year or longer; three were observed more than six months, and six have been followed less than six months at the time of writing.

There have been no recurrences.

Admittedly, the number of cases reported is not large, nor is the period of observation a long one. There is ample time for recurrences; and objections, totally unforeseen may yet arise. However, it is believed that the measure of success so far attained warrants this preliminary report. It is hoped that this technique will be tried by other surgeons and its efficiency thoroughly evaluated.

Case 1 (Fig. 2).—C. F., a housewife aged 68, gave a history of bilateral entropion for the past three years. Corrected vision was 20/30 in the right eye and 20/70 in the left eye. There was slight congenital ptosis of the left upper lid. Examination also disclosed myopic retinal changes in both eyes. The lower half of the left cornea was nebulous and showed punctate

staining. On Sept. 3, 1949, the entropion of the left lower lid was corrected, using the technique described above. The postoperative course was uneventful. On April 11, 1951, the entropion of the right lower lid was similarly corrected. The result is shown in Figure 2.

CASE 2.—B. S., a woman aged 73, gave a history of bilateral entropion of about four years' duration. Correction by means of Snellen sutures two years previously had failed. The best corrected vision was 20/50 in the right eye and 20/60 in the left eye. Both corneas were clear. Both lenses showed nuclear sclerosis. Both conjunctivas showed chronic injection. On Oct. 11, 1949, the entropion of the right lower lid, and on Nov. 15, the entropion of the left lid, were corrected, using the aforedescribed technique. The patient was last seen in January, 1951, when both lids were in normal position.

Fig. 3.—*A* and *B* (case 3): *A*, senile entropion of the right lower lid; *B*, 15 months after operation. The small fibroma of the upper lid was also removed at the time of operation.

*C* and *D* (case 8): *A*, senile entropion of the right lower lid; *B*, two months after repair.

*E* and *F* (Case 10): *A*, bilateral senile entropion; *B*, three months after simultaneous repair of both lower lids.

CASE 3 (Fig. 3*A* and *B*).—M. M., a white woman aged 64, had entropion of the right lower lid. Corrected vision was 20/50 in each eye. Both eyes were white. Ophthalmoscopic examination showed nuclear sclerosis of both lenses. There was also a small pedunculated fibroma of the upper lid over the external canthus (Fig. 3*A* and *B*). On Dec. 9, 1949, the entropion of the right lower lid was corrected, using the above-described technique. The patient was last seen on March 9, 1951. All the lids were in normal position at this time.

CASE 4.—F. L., a white man aged 68, gave a history of intermittent entropion of the right lower lid during the past year. Corrected vision was 20/20 in each eye. The lower conjunctival sac of the right eye was injected. Both corneas were clear. On Feb. 8, 1950 the entropion of the

right lid was repaired according to the technique described. The patient was last seen April 27, 1951.

CASE 5.—J. D., a white woman aged 69, gave a history of bilateral entropion for the past several years. Vision was limited to light perception in the right eye and was 20/60 in the left eye. A mature cataract was present in the right eye, and nuclear sclerosis of the lens, in the left. Both eyes showed chronic conjunctivitis. The corneas were clear. After eradication of the conjunctivitis, the entropion of the right lower lid was corrected, on June 9, 1950. A mild ectropion developed, which was attributed to excision of a tarsal triangle with a base of 7 mm., instead of the usual 5 mm. This righted itself spontaneously in 10 days. On June 23 the entropion of the left eye was corrected in similar fashion. The lids were in excellent position on Sept. 13, 1950. The patient has not been seen since.

CASE 6.—P. D., a man aged 71, gave a history of entropion of the left lower lid for the past "five years or more." There were burning and tearing of the eye, with chronic conjunctivitis and some staining of the lower part of the cornea. Vision was 20/25 in the right eye and 20/50 in the left eye. On June 23, 1950, the entropion was corrected according to the technique described. When the patient was last seen, on April 25, the lid was in normal position.

CASE 7.—T. J., a white man aged 77, gave a history of entropion of the left lower lid of 14 months' duration. Vision was 20/20 in each eye, and both eyes were white and quiet. On Aug. 7, 1950, the entropion was corrected, using the technique described above. When he was last seen, on Jan. 18, 1951, the lid was in normal position.

CASE 8 (Fig. 3*C* and *D*).—D. C., a white man aged 70, gave a history of entropion of the right lower lid of two years' duration. He had had a Wheeler type of correction for this condition a year previously, but the entropion had recurred two months later. Vision was 20/30 in each eye. The right eye showed some conjunctival injection. The cornea was clear. On Sept. 25, 1950, the entropion of the right lower lid was corrected. The patient was last seen on Nov. 22, 1950, with the lid in normal position.

CASE 9.—J. B., a man aged 71, gave a history of entropion of the left lower lid of 18 months' duration. About one year previously he had a Wheeler type of repair of the entropion, which promptly recurred. Vision was 20/20 in each eye. The conjunctival sac of the left eye was injected, but the cornea was clear. On Oct. 23, 1950, the entropion was repaired according to the aforementioned technique. When he was last seen, on April 27, 1951, the lid was in normal position, and the eye was white.

CASE 10 (Fig. 3*E* and *F*.).—R. C., a white man aged 67, gave a history of bilateral entropion of about three years' duration. Vision was 20/50 in the right eye and 20/40 in the left eye. There was bilateral mucopurulent conjunctivitis. The corneas were clear. After treatment of the conjunctivitis, both lower lids were repaired at one time, on Feb. 14, 1951. The patient was last seen on May 2, 1951, when both lower lids were in normal position and both eyes white.

## COMMENT

Over a hundred years ago, von Graefe [16] suggested resection of a small triangle, apex upward, from the base of the tarsus as an adjunct to the correction of cicatricial entropion. More recently, Butler [17] suggested a somewhat similar technic as an office procedure for the relief of senile entropion. There are two serious objections to these suggestions:

1. Failure to strengthen the skin-muscle wall of the lid leaves uncorrected the fundamental abnormality of the condition, i. e., the relaxation of the lid tissues. This makes for recurrences.

2. Simple excision of a triangle from the base of the tarsus leaves a rim of tarsus at the free margin, which causes an unsightly bulge at the lid border when

16. von Graefe, F. W. E. A., cited by Beard,[1a] p. 279.

17. Butler, J. B. V.: A Simple Operation for Entropion, Arch. Ophth. **40**:665 (Dec.) 1948.

the wound is closed. Furthermore, failure to make provision for ample mobility between the tarsoconjunctival and skin-muscle laminas and failure to excise the skin-muscle excess create another bulge in the anterior layer of the lid, which is a cosmetic blemish.

It might be added that, contrary to von Graefe's belief, the procedure is useless in repair of cicatricial (trachomatous) entropion. I have used it in four cases of this type, with complete failure. The reason is not hard to see. Trachomatous entropion is due to a relative shrinkage of the tarsoconjunctival layer, as compared with the usually intact skin-muscle layer. Further resection of tarsal tissue simply serves to exaggerate the difference and aids the inverting mechanism.

On the other hand, it now becomes obvious why Wheeler's orbicularis-transplantation procedure is the most successful of the methods previously devised: By this technique, a horizontal strip is resutured, so as to exert pressure on the lower border of the tarsus and keep it from riding forward. However, there are recurrences, and these are due to the narrowness and consequent weakness of this muscle strip (4 mm.) and to its subsequent stretching.

The procedure I suggest overcomes these objections and has the following advantages:

1. It corrects the fundamental pathologic condition of senile entropion and strengthens the "skeletal" structures of the lid by shortening the base of the tarsus. There is not much likelihood that the tarsus will stretch.

2. The whole of the lower lid is also tautened. Thus, all the components of the lower lid are tightened to prevent deformation of the tarsus.

3. The spindle-shaped incision of skin and muscle assures the greatest amount of tissue resection below the lid border, where the excess of tissue is greatest.

4. The only incision of the skin is at the side of the lid, and hence is practically invisible after healing.

5. The technique is simpler than that of many procedures now in vogue.

## SUMMARY AND CONCLUSIONS

Clinical evidence would seem to indicate that senile entropion is primarily due to the relative enophthalmos and general relaxation of tissues, rather than to localized spasm of the orbicularis muscle.

Relief of this condition should, therefore, be accomplished by strengthening the lid tissues by vertical excision. This is especially true of the tarsus, which is the only firm tissue of the lid.

A technique of procedure to accomplish this is outlined.

This technique was used in the repair of 14 lids of 10 patients.

These 14 lids have been under observation for various periods, from 20 months to two months, with no recurrences.

It would seem logical to term this condition "senile entropion" and to reserve the name "spastic entropion" for the acute, transient types which are amenable to conservative treatment.

11 E. 90th St. (28).

# RETINOPATHY IN DERMATOMYOSITIS

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AMSTERDAM, NETHERLANDS

DERMATOMYOSITIS is a rare disease of unknown etiology. The inflammation of the skin and muscles may take an acute or a chronic course, and death follows in most cases. A new interest in this disease is aroused by the favorable effect of corticotropin (ACTH) in the group of collagenous diseases, of which dermatomyositis forms a part. Reports of ocular involvement are few. Bruce [1] was the first to give a thorough description of the retinopathy in three cases: indefinite yellow-gray patches and hemorrhages both in the superficial and in the deep retinal layers. Two of the patients recovered, and the retinopathy disappeared. Histological examination of the posterior segment in his third case showed groups of cytoid bodies in the nerve-fiber layer, albuminous deposits in the outer layers, and small hemorrhages. Lisman [2] reported another case with retinal exudates, mostly superficial and of transient character. Examination of the sectioned eye showed hyaline and lipid changes in the outer plexiform layer, and hemorrhages. London [3] described another case of retinopathy, which disappeared after three weeks, while the patient recovered from his dermatomyositis.

It must be emphasized that in all these cases the diagnosis of dermatomyositis was firmly established by the clinical symptoms, and in all but one case by histological examination also. The kidneys were not involved; the blood pressure was normal; sepsis and blood dyscrasias were absent. Another collagenous disease in which a similar retinopathy may be found is lupus erythematosus.[4] From this disease the condition in the previous cases could be well differentiated, however. There is ample evidence, therefore, that dermatomyositis may be accompanied with retinopathy. The associated fundus picture seems to be nonspecific; and, especially for differentiation of this disease, lupus erythematosus, and septic conditions, other clinical symptoms must be relied upon. Because of the rarity of dermatomyositis, I feel justified in reporting the following case.

## REPORT OF A CASE

Mrs. M. L. B., aged 49, was admitted July, 1949, to the University Clinic for Internal Medicine in the Binnengasthuis (Director, Prof. Dr. J. G. G. Borst), with a febrile disease of seven weeks' duration. The joints of the feet and wrists were tender and swollen. The blood

1. Bruce, G. M.: Retinitis in Dermatomyositis, Tr. Am. Ophth. Soc. **36**:282-297, 1938.

2. Lisman, J. V.: Dermatomyositis with Retinopathy: Report of a Case, Arch. Ophth. **37**:155-159 (Feb.) 1947.

3. London, R. D.: Case 3. Dermatomyositis, in report on Conference at the Mount Sinai Hospital of New York, March 24, 1949, J. Pediat. **36**:817-820 (June) 1950.

4. Maumenee, M. D.: Retinal Lesions in Erythematosus, Am. J. Ophth. **23**:971-981 (Sept.) 1940.

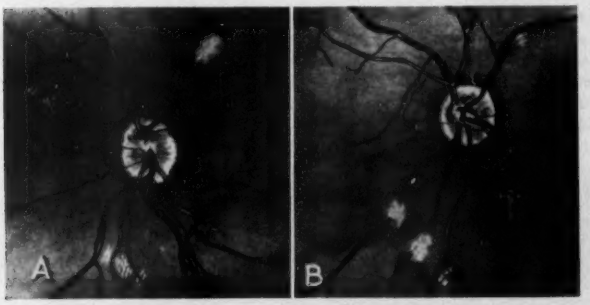


Fig. 1.—Fundus of the eyes on Sept. 9: *A*, right eye; *B*, left eye.

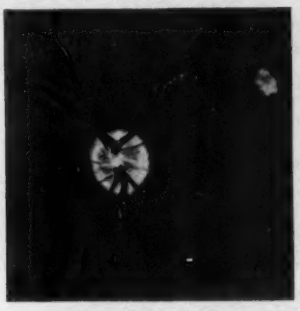

Fig. 2.—Fundus of the right eye on Oct. 11.

Fig. 3.—Patch of retinopathy in the right eye; hematoxylin-eosin stain.

formula was characteristic of a toxic condition; the sedimentation rate was 28 to 55 mm. The urine and blood pressure were normal. Transitory exanthems were attributed to use of the medicaments aminopyrine (pyramidon®) and sodium salicylate, which failed to produce any improvement, however. Three weeks after her admission there were increasing edema and weakness of the muscles of the hands. Though blood cultures were sterile, penicillin treatment gave considerable improvement in the general situation. The edema fluid had a high protein

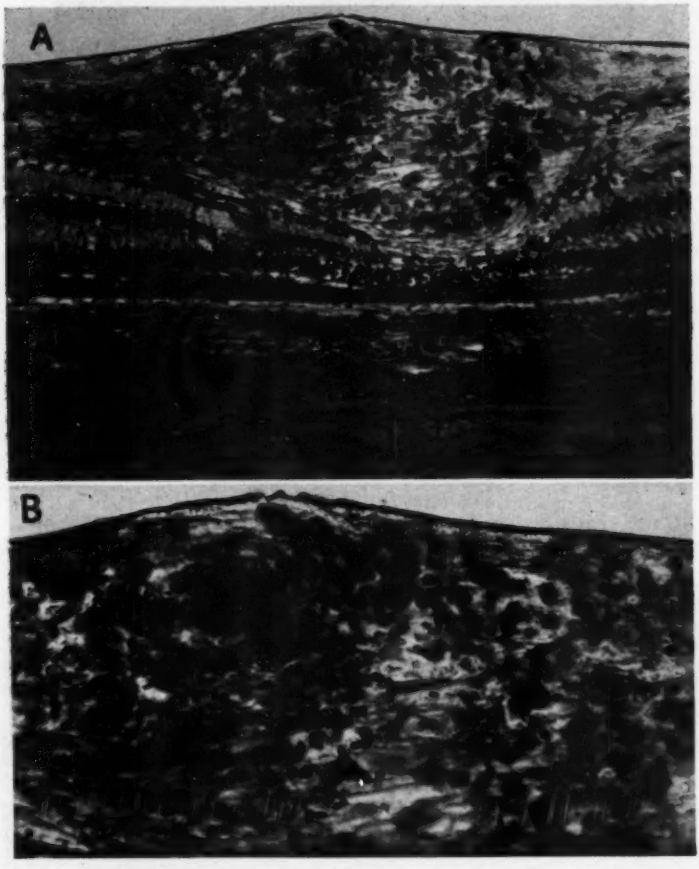


Fig. 4.—Higher magnifications of the patch of retinopathy shown in Figure 3; hematoxylin-eosin stain.

content. It was then assumed that the disease was a septic one. Injections of penicillin, 4,000,000 units a day, however, did not improve the toxic blood formula (20,000 leucocytes, many myelocytes, and metamyelocytes) or the high sedimentation rate (119 to 140 mm.). Again, transitory exanthems and erythema developed. In addition to massive edema of the forearms and the legs, the muscles of the upper arms and legs became weak. Creatinine excretion was low (457 mg. in 24 hr., 1.5 gm. being normal). Creatine excretion was increased (337 mg. in 24 hr., 150 mg. being normal). The skin showed desquamation and atrophy. All clinical signs now pointed to the diagnosis of dermatomyositis (September, 1949), which was confirmed by

histological examination (biopsy) of skin and muscle tissue. Steady deterioration followed; finally, tachycardia and superficial respiration developed (probably the heart and respiratory muscles were diseased), and death soon followed (Jan. 10, 1950).

The first ophthalmological examination took place on Sept. 9. In both eyes (Fig. 1) a number of grayish-white patches and groups of small white spots were seen in the nerve fiber layer. There were no hemorrhages, and the blood vessels of the retina were normal. At first, in accord with the evaluation of the other clinical signs, the retinopathy was considered septic. The fundus picture, however, fitted as well the diagnosis of dermatomyositis, which was established three weeks later.

On Oct. 11 the fundus showed the same patches, but they were thinner and had decreased in size. On Dec. 6 the retinal patches in the left eye had completely disappeared. In the retina of the right eye a new, but superficial, patch was visible, as well as a group of small white spots (Fig. 2).

*Pathologic Report* (from the laboratory of Dr. R. van Dam).—The muscle fibers of the heart were narrow and showed fragmentation and fibrosis in several places, without signs of inflammation. In the skin, infiltrations of lymphocytes and perivascular infiltrations of plasma cells were observed.

The fibers of the psoas and intercostal muscles showed loss of fibrillar structure, vacuoles and poor staining, and interstitial edema with interstitial infiltration of lymphocytes and plasma cells. Only in a few places was proliferation of cells found, probably of the sarcolemma.

The blood vessels and the nerves showed no abnormalities. The right eye, in which retinopathy was found on the last examination, five weeks before, could be obtained after death for microscopic examination (from the laboratory of Prof. Dr. A. Hagedoorn).

The intrinsic muscles of the eye showed no abnormalities. In the sections, the medial and lateral rectus muscles could be examined; but, apart from slight lymphocytic infiltration in one place, no definite changes were present. The sclera, choroid, and optic nerve were normal. In the retina cytoid bodies were lying in the nerve-fiber layer (varicose or ganglion-like swelling of fibers). This area obviously corresponded to the patch of retinopathy seen ophthalmoscopically. It also contained an albuminous deposit and showed separation of paralleling nerve fibers. Hemorrhages and cellular infiltrations were absent. It formed a considerable thickening and resulted in a pushing away of adjacent layers.

SUMMARY

A third case of retinopathy associated with dermatomyositis confirmed histologically is reported.

# Registry of Interesting Cases

*It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.*

## DIVERGENCE PARALYSIS AND PARALYSIS OF THE NEAR REFLEX ASSOCIATED WITH A MALNUTRITION SYNDROME (PRESUMABLY WERNICKE'S POLIOENCEPHALITIS)

L. C., a man aged 29, had been examined intermittently over a four-year period.

At the age of 20 the patient had an uncomplicated operation for ruptured appendix. He was then well until the age of 22, when severe diarrhea, anorexia, and vomiting developed. The onset was acute, but the symptoms became chronic, associated with great loss of weight and accompanied with bouts of distention, cramps, and fever. At the age of 25 a laparotomy was performed, and a "peptic ulcer" is said to have been "sutured." Three weeks after the operation the wound opened, resulting in a persistent fecal fistula. The patient was described as having been profoundly debilitated at this time.

Two months after the operation the patient was admitted for the first time to the Massachusetts General Hospital, and an ileotransversostomy was done. After this he was put on a regimen of intravenous feedings for a week, followed by a high-calory, high-vitamin diet, with only partial success. He remained cachectic, and there developed tetany and persistent numbness of his fingers. The blood calcium was as low as 5 mg. per 100 cc.; the vitamin-A level of the blood was 0.4 unit per cubic centimeter (normal 0.3 to 1.0 unit per cubic centimeter), and no carotenoids were demonstrable in the blood (normal, 1 to 3 units per cubic centimeter). The patient was thought to have multiple vitamin deficiencies for at least several months after the operation.

The patient first complained of ocular symptoms one month after the colostomy. He stated that his eyes hurt him on attempting to read. A superficial examination of the eyes revealed nothing abnormal, and no further examination was made until three months later. In the meantime, there developed considerable lethargy, vertigo, incoordination of the arms and legs, diplopia, and difficulty with speech. Several convulsive episodes were interpreted as tetany. Neurologic examination showed marked ataxia of all four extremities, gross dysarthria of speech, ocular signs, to be described, and normal reflexes. A diagnosis was made of polioencephalitis hemorrhagica of Wernicke.

The eyes showed an esotropia of approximately 15 degrees, which was constant for all horizontal directions of gaze. There were homonymous diplopia for all distances greater than 0.5 m., monopia over a range of 15 to 25 cm., and crossed diplopia for distances less than 0.25 m. There were also a greater than normal nystagmus on gaze to either side and an ill-sustained vertical nystagmus on looking upward. The pupils showed prompt and full reaction to light but no reaction to a near stimulus. Unfortunately, the accommodative amplitude was not tested. The rest of the ophthalmologic examination revealed nothing abnormal, and the ophthalmologic diagnosis was divergence paralysis together with associated insufficiency of convergence and pupillary areflexia for near.

The patient was given supplemental vitamin B therapy and showed prompt improvement in ocular signs, as well as in the numbness, tingling, and ataxia.

Examination of the eyes two months after that noted above showed orthotropia for distance. There were, however, a gross insufficiency of convergence and a crossed diplopia for objects less than 25 cm. from the patient. The pupils were 7 mm. in diameter and showed a prompt miosis for light but still no reaction for near. The near point of accommodation was approxi-

mately 50 cm.; for distance the patient was unable to overcome a —1.00 sphere. The nystagmus previously noted was now manifest only as a minimal horizontal nystagmus on extreme gaze to either side. A diagnosis was made of residual paralysis of the near reflex. A correction of +2.00 sph. was given for near, with complete relief of symptoms.

The patient was reexamined after wearing the glasses for one month. The near point of convergence had improved to 10 cm., and accommodation had improved to 8 D. The patient had no difficulty in reading without his glasses. The pupils, however, showed no reaction to near. There had been considerable gain in weight and improvement in his general condition.

One year later the patient again complained of asthenopia and on examination was found to have diplopia for objects less than 35 cm. away; accommodation was reduced to 3½ to 4 D. There was still no reaction of the pupil to near. Blepharitis was also present to a mild degree, and the lower halves of the corneas showed considerable keratitis epithelialis. The patient had on a fat-free diet, and the blepharokeratitis was believed to be due to vitamin-A deficiency. The convergence and accommodative insufficiency were thought to be attributable to the debility, rather than to a recurrence of the paresis of the near reflex. In any case, considerable subjective improvement occurred with supplemental vitamin-A therapy, and the patient did not again seek ophthalmological help.

At the time of writing, five years after the episode described above, the patient was called back for reexamination. Accommodation for near was 5 D. in both eyes, which is slightly subnormal for the age of 34; the pupils reacted promptly to light and a near stimulus. The near point of convergence was 10 cm., and the eyes showed only a few degrees of esophoria for distance.

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## AN UNUSUAL PIGMENTED TUMOR OF THE IRIS

The case is recorded of a peculiar pigmented tumor of the iris, which, although not the usual malignant melanoma, was locally invasive and could be expected to have destroyed the eye.

*History*—A girl aged 7 years had a history of a small black spot at 6 o'clock on the iris of the right eye, first noticed at the age of 3 months. Originally the lesion was the size of a pinhead and was located midway between the limbus and the pupillary margin. The lesion became progressively larger and although it had doubled in size in the preceding six months, the parents were not alarmed until the right eye became red, two weeks prior to the child's admission. Examination revealed a blonde, blue-eyed child with fair skin and injection of the bulbar conjunctiva of the right eye. There was a black, nodular mass on the iris of the right eye from 5 to 7 o'clock, extending from the limbus over the pupillary margin, but not attached to the ruff of the iris. The anterior chamber was deep, but the summit of the mass touched the posterior surface of the cornea. There were an aqueous flare and floating cells in the anterior chamber. Fine pigment dusting on the cornea and on the iris obscured the architecture of the iris. The pupillary margin was flattened in the area of the tumor. The lens was clear and the fundus not remarkable. Vision was 20/20 in each eye. The left eye was normal. An excisional biopsy was done. At operation the mass was found to be somewhat pedunculated, so that there was 1 to 2 mm. of iris base not grossly involved by the tumor. Because of the invasive and anaplastic appearance of the tumor microscopically and of some uncertainty as to its total removal, the eye was enucleated two days later. At the time of writing, the child is in good health, and there has been no evidence of metastasis.

*Gross Appearance* (Eye Pathology No. 50-243).—The specimen was a black fragment of tissue, measuring 6 mm. in its greatest diameter. The tissue was fixed in dilute solution of formaldehyde U. S. P. and embedded in paraffin.

*Microscopic Study.*—The specimen consisted of a radial section of iris from which a large, heavily pigmented mass arose, involving the dilator layer of epithelium and the entire thickness of the stroma. The tumor consisted of heavily pigmented cells, separated by empty spaces, with little or no stroma. The cells varied widely in size and shape, usually possessing abundant irregular or rounded cytoplasm and delicate protoplasmic processes. The nuclei were generally rounded or oval, some with nucleoli and others vesiculated with scattered chromatin. Many of the cells were multinucleated. The tumor was highly vascular, containing many thin-walled blood vessels. The principal mass of the tumor was located somewhat nearer the base of the iris than the pupillary margin, and in this region the dilator layer of epithelium was disturbed, although the pigment epithelium was not involved. The tumor was definitely invasive in its extension toward the ciliary body, but various sections disclosed no tumor cells in the enucleated eye. Special stains revealed little or no fibrous stroma or argyrophil-fiber content.

*Comment.*—It was not possible to identify the origin of this tumor with any certainty. The heavy pigmentation suggested that the neoplasm arose from one of the normally pigmented cells of the iris, that is, the pigment epithelium, the dilator epithelium, the clump cells, or the branched chromatophores. Serial sections failed to demonstrate involvement of the pigment epithelium at any point, so that this layer would seem to be eliminated from consideration. Tumor cells

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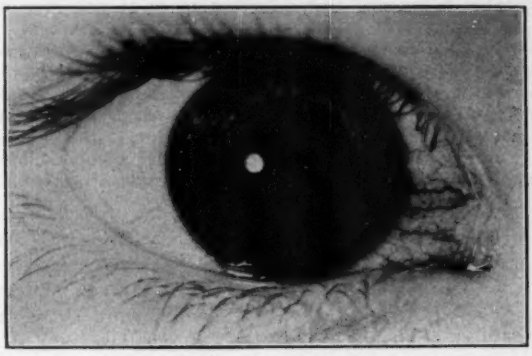

Fig. 1.—Clinical appearance of tumor at time of the first visit.

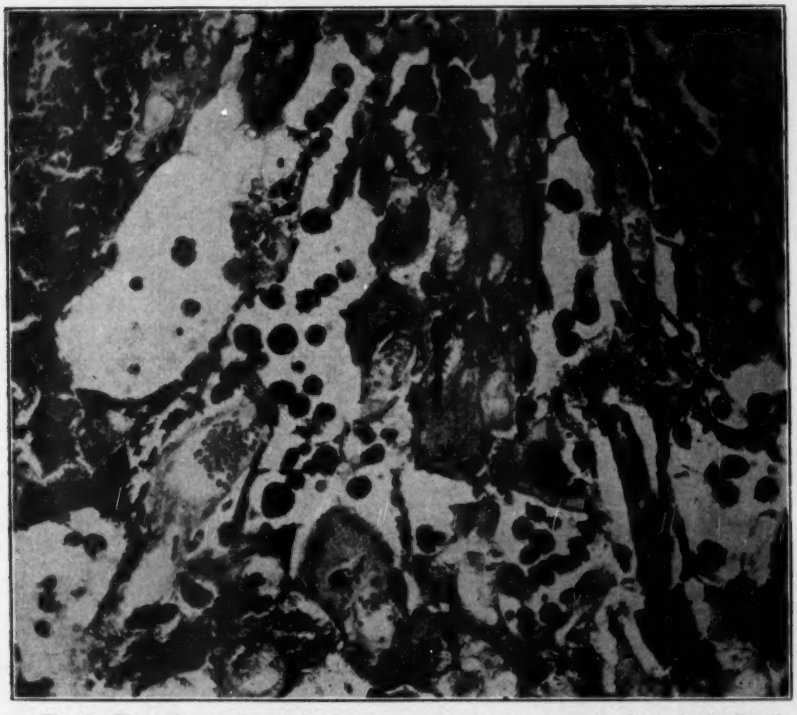

Fig. 2.—Photomicrograph showing highly vascular tumor, composed of anaplastic, heavily pigmented, often multinucleated cells with empty spaces between and little stroma.

replaced the dilator epithelium over a considerable area, but they bore no recognizable relationship to mature dilator epithelium or to primitive medullary epithelium. There was no evidence of myofibrils. In some respects, the manner of pigmentation resembled that of the clump cells in that the granules tended to be large and very dark, frequently covered the nucleus, and were highly resistant to bleaching. However, the main mass of the tumor was located in an area distant from those regions where clump cells are normally seen. The delicate protoplasmic processes of many of the cells suggested a relationship to the branched chromatophores, and it has been the opinion of the majority of ophthalmic pathologists who have examined this tissue that the tumor probably arose from the branched chromatophores of the iris.

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# Annual Reviews

## PHYSIOLOGIC CHEMISTRY OF THE EYE

### A Review of Papers Published During 1950

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PAPERS selected for this review include not only those which deal directly with the chemistry of various parts of the eye but also some concerned with related subject matter involving various experimentally induced changes in ocular tissues, from which certain accessory information of a chemical nature may be derived.

### GENERAL SURVEY [1]

A noteworthy contribution to the ophthalmologic literature of 1950 is a textbook by Adler [2] entitled "Physiology of the Eye: Clinical Application." This work gives a comprehensive review of the chemistry of the eye, with particular emphasis on its physiologic significance.

The further localization of various compounds within the eye has continued to be a chief interest of investigators. The application of histochemical techniques has been particularly useful for conducting studies of this kind.

The presence of choline acetylase in the iris, ciliary body, and retina of the cat and rabbit is suggested by experiments performed by deRoetth,[3] who demonstrated the synthesis of acetylcholine by use of powder obtained from acetone extraction of these tissues. The same worker,[4] using Hestrin's new colorimetric method,[4a] also determined the cholinesterase activity of tissues and fluids of the eyes of various animals, including man. The highest enzyme activity was observed in tissues containing muscles or nerves, e.g., the iris, ciliary body, and retina. The aqueous and vitreous humors contained only traces of the enzyme. The hydrolysis pattern for most of the tissues was typical of that of the specific cholinesterase. Nonspecific cholinesterase was observed in the ciliary body of the horse and in the serum and secondary aqueous humor of the cat. The ciliary body of the normal human eye contained 355 units of acetylcholinesterase, i.e., sufficient cholinesterase to hydrolyze 355 mg. of acetylcholine per gram of tissue per hour; the iris contained 30 units, and the extraocular muscles, 44 units.

The iris and ciliary body of eyes with absolute glaucoma and of degenerated atrophic globes contained less cholinesterase than the comparable structures of normal eyes, although no experimental evidence was elucidated to show a causal relation.

1. Papers considered under this heading deal with chemistry in various parts of the eye and will not be reconsidered under separate headings.

2. Adler, F. H.: Physiology of the Eye: Clinical Application, St. Louis, C. V. Mosby Company, 1950.

3. deRoetth, A., Jr.: Choline Acetylase Activity in Ocular Tissues, Arch. Ophth. **43**:849 (May) 1950.

4. deRoetth, A., Jr.: Cholinesterase Activity in Ocular Tissues and Fluids, Arch. Ophth. **43**:1004 (June) 1950.

4a. Hestrin, S.: Reaction of Acetylcholine and Other Carboxylic Acid Derivatives with Hydroxylamine, and Its Analytical Application, J. Biol. Chem. **180**:249, 1949.

The relative activity rates for choline acetylase and cholinesterase in the various tissues were similar. The retina of the rabbit contained five times as much cholinesterase as the iris and ciliary body and six times as much choline acetylase.

Using histochemical technique, Koelle and Friedenwald [5] showed that the cholinesterase activity of the retina appears to be greatest in the internuclear layer and the immediately adjacent portions of the plexiform layer, the heaviest concentrations being noted in the horizontal and bipolar cells. In the ciliary processes, the cholinesterase activity appeared to be concentrated between the two layers of the epithelium. Sections of ciliary-body muscle revealed diffuse staining of the muscle fibers and their nuclei. Fibers in the posterior surface of the iris and in the walls of the vessels were heavily stained.

The enzyme concerned with the hydrolysis of glucuronide linkage (glucuronidase) was localized in the ciliary body, the conjunctival mucous membrane, and the cells of the cornea.[6] It is also distributed throughout the cells in the Harderian and lacrimal glands. The high activity of glucuronidase observed in the ciliary epithelium suggested to the authors that this tissue may be a site of synthesis of vitreous mucoid.

Using the histologic technique of Hotchkiss and Friedenwald, which indicates the presence of polysaccharides in various ocular tissues by the degree of staining, Day [7] observed that the basement membranes, such as Descemet's (posterior elastic) and Bruch's (anterior elastic) membranes, and the capsule of the lens stained intensively. The corneal epithelium and the outer half of the rod-and-cone layer of the retina exhibited slightly less intense staining. The internal limiting membrane of the retina stained deeply and in this respect differed from the outer limiting membrane. The corneal stroma, the supporting structure of the optic nerve, and the ciliary muscle stained less strongly. The sclera, the inner half of the rod-and-cone layer, and the vitreous humor stained faintly. Other structures stained little or not at all. No conclusion could be drawn as to the interesting question of whether the ciliary body is the site of formation of hyaluronidase.

When ascorbic acid was injected into mice and rabbits, the substance was observed to be concentrated in the cornea, particularly the endothelium, and in the lens and uvea, except for the epithelium of the ciliary body.[8] The sclera, retina, and optic nerve contained little ascorbic acid. The absence of reduced ascorbic acid in the epithelium of the ciliary body is cited as further evidence for the thesis that ascorbic acid is present in this structure only in the oxidized form, whence it enters the posterior chamber, to be reduced to ascorbic acid by the lens. The validity of this concept has been questioned [9] (section of "Aqueous Humor").

By using iodine, von Sallmann [10] extended his studies on the demonstration of the topographic relation of ions within the various structures of the eye. It was

5. Koelle, G. B., and Friedenwald, J. S.: The Histochemical Localization of Cholinesterase in Ocular Tissues, Am. J. Ophth. **33**:253, 1950.

6. Becker, B., and Friedenwald, J. S.: The Histochemical Localization of Glucuronidase in Ocular Tissues and Salivary Glands, Am. J. Ophth. **33**:673, 1950.

7. Day, R.: Polysaccharides in Ocular Tissue, Am. J. Ophth. **33**:224, 1950.

8. François, J., and Rabaey, M.: Localisation histo-chimique de l'acide ascorbique reduit dans l'œil de certains mammifères, Ann. ocul. **183**:829, 1950; abstracted, Ophth. Lit. **4**:489, 1951.

9. Kinsey, V. E.: Dehydroascorbic Acid-Ascorbic Acid in the Aqueous Humor of Rabbits, Am. J. Ophth. **33**:257, 1950.

10. von Sallmann, L., and Dillon, B.: Studies of the Eye with Radioiodine Autographs, Am. J. Ophth. **33**:429. 1950.

shown by radioautographic studies that iodine administered systemically tends to accumulate to a greater extent in the cornea than in the other parts of the eye. The relative distribution of activity of iodine 24 hours after intraperitoneal injection, in terms of percentage activity of plasma, was observed to be as follows: aqueous humor, 44; vitreous humor, 20; cornea, 64; sclera, 51, and anterior uvea, 48. The results von Sallmann obtained with iodine differ from those which he obtained previously with sodium and phosphorus. Sodium was confined mainly to the extracellular space, and phosphorus was characterized by intracellular penetration. Quantitative measurements of the density of radioautographs expressed in terms of radioactivity were obtained by using as reference standard agar disks containing known concentrations of the radioactive indicator. The results obtained with this method of measurement correspond with those obtained with the Geiger-Müller counter.

Partial amino-acid compositions (50%) of the corneal stroma and epithelium, sclera, vitreous humor, and retina of bovine eyes were determined by microbiologic assay by Schaeffer and Murray.[11] The concentrations of amino acids present in the individual proteins (mucoid, collagen, and elastin) of the corneal stroma and sclera were also obtained. The amino-acid distribution of the cornea and sclera as a whole appeared to be quite similar, although it differed in several respects in the individual protein fractions of these tissues.

A general investigation of amino-acid metabolism in ocular tissues by de Vincentiis and Auricchio [12] showed that the cornea, lens, retina, and choroid all contain amino acid oxidase and hence are capable of deaminating amino acids. The concentration of keto acids in ocular tissues was observed to increase in the presence of arsenic trioxide, suggesting that normally these tissues are capable of further breakdown of amino acids. No evidence was obtained to indicate the presence of transaminase (aminopherase). This observation would seem to account in part for the peculiar dependence of ocular tissues on a supply of all the amino acids. Whereas transamination appears to be lacking in ocular tissues, enzymes capable of transmethylation, as exemplified by the conversion of guanidinacetic acid to creatine, were found in the retina and, to a less degree, in the cornea.[13]

### TEARS

The "true" glucose content of tears removed from normal human subjects was found to be 2.5 mg. per 100 ml.[14] The glucose accounts for a little less than one-half the total reducing substances present. Incidentally, the authors observed that in the serums of the same patients the glucose accounted for 80% of the total reducing substances present.

The chloride content of tears obtained after profuse lacrimation (tear gas) was 110 mM. per liter, whereas that of the first 0.01 ml. of tears which appeared was 135.5 mM. per liter. The authors point out that, while the chloride content is not

11. Schaeffer, A. J., and Murray, J. D.: Amino Acid Composition of Tissue Proteins of the Cornea, Sclera, Vitreous and Retina, Arch. Ophth. **44**:833 (Dec.) 1950.

12. de Vincentiis, M., and Auricchio, G.: Sur le metabolisme des acides aminés dans les tissus oculaires, Acta ophth. **28**:7, 1950; abstracted, Excerpta Med. XII **4**:488, 1950.

13. de Vincentiis, M., and de Berardinis, E.: Sui processi di transmetilazione nei tessuti oculari, Rass. ital. ottal. **19**:237, 1950; abstracted, Ophth. Lit. **4**:488, 1951.

14. Giardini, A., and Roberts, J. R. E.: Concentration of Glucose and Total Chloride in Tears, Brit. J. Ophth. **34**:737, 1950.

a good index of the tonicity of tears, the result suggests that tears may be hypertonic to aqueous humor. They observed the total solids to be 1.84 per 100 ml., a value which corresponds closely to that obtained in another study of human tears.[15]

The osmotic activity of artificially stimulated tears was measured directly and reported by Schaeffer[16] to be equivalent to "160±" mM. of sodium chloride per kilogram of water. He observed that the osmotic activity of both the aqueous humor and the plasma in four subjects was essentially identical with that of tears and concluded that there are no differences in osmotic pressure on the two sides of the cornea which could account for movement of fluid across the cornea in either direction. His conclusions based on these determinations are questionable, however, because the method employed had a limit of accuracy of approximately $\pm_{10}$ mM. per kilogram of water,[17] a value in excess of that required to reveal differences in osmotic pressure of body fluids which would have physiologic significance.

Tears of the normal human subjects stimulated by exposure to benzyl chloride were observed to contain from 800 to 2,500 units of lysozyme activity per milliliter, where one unit is defined as the amount of enzyme required to reduce the viscosity of a solution of mucopolysaccharides to one-half its original value in 10 min.[18] The lysozyme activity of the tears of males and females was the same, but it varied widely in any one subject from time to time. In pathologic conditions in which epiphora was a prominent feature there was usually a reduction of the amount of enzyme present. This reduction also occurs in patients having corneal dystrophies.

### CORNEA

The mucopolysaccharide content of the cornea was observed to be 3.8%.[19] The water-soluble mucopolysaccharide was not present in free state but formed a definite complex with protein. Neither this complex nor the free mucopolysaccharide could be hydrolyzed by hyaluronidase, suggesting that these compounds should be described as mucoitin sulfate, rather than as hyaluronosulfate.

Knowledge that the repair of collagenous tissues is dependent upon an adequate supply of ascorbic acid led Campbell and Ferguson[20] and Campbell, Ferguson, and Garry[21] to determine the rate of repair of heat-damaged corneas in normal and scorbutic guinea pigs. The corneas of scorbutic guinea pigs required 30% longer to regenerate after damage to the anterior two-thirds of the stroma than did those of guinea pigs fully saturated with ascorbic acid. Moreover, in scorbutic guinea pigs a structural weakness of the wound persisted for as long as three weeks after injury, as compared with 11 days in the guinea pigs saturated with ascorbic acid. Further work on this subject was performed by Boyd and Campbell,[22] who compared the

15. Smolens, J.; Leopold, I. H., and Parker, J.: Studies of Human Tears, Am. J. Ophth. **32**:153 (June, Pt. 2) 1949.

16. Schaeffer, A. J.: Osmotic Pressure of the Extraocular and Intraocular Fluids, Arch. Ophth. **43**:1026 (June) 1950.

17. Sufficient to produce a pressure of approximately 350 mm. of mercury.

18. Regan, E.: The Lysozyme Content of Tears, Am. J. Ophth. **33**:600, 1950.

19. Woodin, A. M.: The Corneal Mucopolysaccharide, Biochem. J. **47**:xxxvii (Sept.) 1950.

20. Campbell, F. W., and Ferguson, I. D.: Role of Ascorbic Acid in Corneal Vascularization, Brit. J. Ophth. **34**:329, 1950.

21. Campbell, F. W.; Ferguson, I. D., and Garry, R. C.: Ascorbic Acid and Healing of Heat Injuries in the Guinea-Pig Cornea, Brit. J. Nutrition **4**:32, 1950.

22. Boyd, T. A. S., and Campbell, F. W.: Influence of Ascorbic Acid on the Healing of Corneal Ulcers in Man, Brit. M. J. **2**:1145, 1950.

rate of healing of corneal ulcers in men given 1.5 gm. of ascorbic acid daily with the rate in those not so saturated. No significant difference in the rate of healing of superficial lesions of the cornea was seen, but deep ulcers healed significantly more rapidly in the group whose diets were supplemented with large doses of ascorbic acid. The authors suggested that there might be a localized area around the site of degenerating corneal collagen where the ascorbic-acid concentration decreases to below the optimal for rapid healing.

While the rate of repair of the epithelium of the cornea does not appear to be influenced by the local administration of ascorbic acid, Schaeffer [23] showed that the epithelium of corneas to which a mixture of amino acids was applied locally regenerated 30 hours sooner than that of control eyes to which saline solution was administered. Omission of the cystine from the amino-acid mixture removed the stimulating effect on epithelization. Methionine, an essential amino acid, was unable to substitute for cystine. The author concluded that the epithelization-stimulating effect of the amino-acid mixture was due mainly to its cystine content. This conclusion is questionable, however, in the absence of information concerning the effect of the withdrawal of other amino acids from the mixture or the use of cystine alone.

The author noted that the growth-stimulating effect of the amino acids decreased when the osmotic concentration of the solution in which the acids were dissolved was lower than 0.9%, or higher than 1.3%, equivalent of sodium chloride solution. From this observation, he concluded that it is undesirable for a fluid applied to the cornea to be isosmotic with a 1.4% saline solution, i. e., that commonly recommended. A clinical test of the amino-acid combination was made, but quantitative evaluation was not attempted because of the limited numbers of cases investigated.

Further evidence of the importance of the tonicity of the fluid bathing the anterior surface of the cornea with regard to maintaining the cornea in its normal deturgesced state is presented by von Bahr,[24] who measured the effect of solutions of different osmotic pressures on the thickness of the living cornea. He noted that the thickness of the human cornea after being bathed with distilled water for 30 min. increased from the normal 0.565 mm. to 0.60 mm. Similar results were obtained with rabbit eyes. The author also reports that the thickness of rabbit corneas decreased after application of solutions of sodium chloride of 5, 2, and 1.5%. Replacement of the aqueous humor with air increased the magnitude of the changes in the corneal thickness, suggesting that there was a counterbalancing effect of the aqueous humor. Von Bahr agrees with the thesis of Cogan and Kinsey [25] that there is a circulation of fluid in the cornea caused by differences in osmotic pressure of the solutions bathing the epithelium and the endothelium.

Stern,[26] in a review article which is primarily of clinical interest, emphasizes the fact that if riboflavin is withheld sufficiently long to produce a low concentration in the tissues corneal vascularization will always result. He also points out that limbic congestion and circumcorneal injection are not pathognomonic of ariboflavinosis.

23. Schaeffer, A. J.: An Attempt to Influence Corneal Wound Healing by Local Application of Certain Amino Acids, Am. J. Ophth. **33**:741, 1950.

24. von Bahr, G.: Measurements of the Effect of Solutions of Different Osmotic Pressure on the Thickness of the Living Cornea, Tr. Ophth. Soc. U. Kingdom (1948) **68**:515, 1949.

25. Cogan, D. G., and Kinsey, V. E.: The Cornea: V. Physiologic Aspects, Arch. Ophth. **28**:661 (Oct.) 1942.

26. Stern, J. J.: The Ocular Manifestations of Riboflavin Deficiency, Am. J. Ophth. **33**:1127, 1950.

The interrelation of growth and metabolism of the cornea is reviewed by Friedenwald.[27]

Respiration of the cornea was again investigated.[28] The oxygen uptake varied from species to species, increasing in the following order: rat, guinea pig, rabbit, man, and cat. The oxygen consumption of this tissue decreased to about one-third of normal after preservation by Filatov's method for 10 days.

DeRoetth [29] observed that the cornea has a respiratory quotient of 1.0, indicating that carbohydrate is the chief substrate used by this tissue. He observed that the oxygen uptake for beef corneas in phosphate-buffered saline solution, Ringer's solution, or Ringer-dextrose solution, in either air or 100% oxygen, varied from —0.50 to —0.60 $QO_2$ unit (microliters of oxygen absorbed per milligram dry-weight tissue per hour). He also altered the pH of the medium from 5.7 to 7.5 apparently "by adding small amounts of sodium bicarbonate to Ringer's solution" and reported that the difference in pH was without effect on the respiratory activity. Because of the likelihood that the pH changed during the course of the experiment, as a result both of loss of carbon dioxide and of the buffering action of the cornea, the conclusion that corneal metabolism is uninfluenced by the hydrogen-ion concentration within these limits of the pH is questionable.

The cornea apparently contains enzymes necessary to hydrolyze fatty-acid esters.[30]

Interesting data on the source of entrance of several inorganic ions to the cornea are presented by Potts and Johnson.[31] These authors measured the rate of entrance of radioactive phosphorus, sodium, iodine, and cesium from the blood stream, subconjunctiva, anterior chamber, and precorneal tear film by determining the rate of accumulation of the radioactive materials in various parts of the cornea. The results indicated that the limbal vascular plexus plays a predominant role in supplying ions to the cornea. A small but significant amount of the substances studied was observed to pass through the anterior and posterior corneal surface membranes. The entrance of ions into the cornea appeared to be governed by factors other than those which control the loss of these ions from the blood stream; each ion studied acted in an individual manner. The concentration of the various ions found in the tears ranged from 0.2 to 300% of the blood level, the extremes being for phosphorus and iodine, respectively. As von Sallmann also observed, iodine accumulated in the cornea to a greater extent than sodium, relative to the content of both these ions in the aqueous humor.

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27. Friedenwald, J. S.: Recent Studies on Corneal Metabolism and Growth: A Review, Cancer Res. **10**:461, 1950.

28. Epshteyn, M. M.: Respiration of Fresh and Preserved Cornea, Vestnik. oftal. **29**:22, 1950; abstracted, Ophth. Lit. **4**:490, 1951.

29. deRoetth, A., Jr.: Respiration of the Cornea, Arch. Ophth. **44**:666 (Nov.) 1950.

30. de Berardinis, E., and de Vincentiis, M.: Contributo sperimentale allo studio del ricambio del tessuto corneale. Sul metabolismo lipidico della cornea, Rass. ital. ottal. **19**:164, 1950; abstracted, Excerpta Med. XII **5**:137, 1951.

31. Potts, A. M., and Johnson, L. V.: Nutritional Supply of Corneal Regions in Experimental Animals: I. The Supply of Some Inorganic Ions, Am. J. Ophth. **33**:405, 1950.

## AQUEOUS HUMOR

A review of the literature on the dynamics of the aqueous humor and its significance with regard to the intraocular pressure is presented by Davson.[32]

The hydrogen-ion concentration, osmotic pressure, and chemical composition of the aqueous humor and plasma (arterial blood), withdrawn from rabbits at essentially the same time, were determined by Kinsey.[33] The pH of the aqueous humor was observed to be 7.57, a value which exceeds that of the plasma by 0.17 unit. The osmotic pressure of the aqueous humor exceeded that of the plasma of freshly drawn samples by approximately 3 mM. per kilogram of water equivalent of sodium chloride. The osmotic pressure of the aqueous humor and plasma and the total concentration of dissolved substances of pooled samples determined chemi-

*Composition of the Aqueous Humor and Plasma of the Rabbit*

| Dissolved Substance | Aqueous Humor (72 Eyes) mM./Kg. $H_2O$ | Plasma (Arterial) (36 Animals) mM./Kg. $H_2O$ | Ratio Aqueous / Plasma |
|---|---|---|---|
| **Anions** | | | |
| Chloride | 107.9 | 113.8 | 0.95 |
| Bicarbonate* | 31.9 | 21.9 | 1.45 |
| Ascorbate | 1.2 | 0.1 | 12 |
| Lactate | 8.8 | 6.6 | 1.3 |
| Phosphate | 0.7 | 1.2 | .... |
| Sulfate† | 0.6 | 1.2 | .... |
| Protein | <0.05 | 2.6 (approximately) | .... |
| Total | 151.1 | 146.8 | 1.04 (diffusible ions only) |
| **Cations** | | | |
| Sodium | 143.0 | 146.0 | 0.98 |
| Potassium | 4.7 | 4.8 | .... |
| Calcium (diffusible) | 1.4 | 1.8 | .... |
| Magnesium‡ | 0.5 | 0.9 | .... |
| Total | 149.6 | 153.5 | 0.973 |
| **Nonelectrolytes** | | | |
| Carbonic acid | 1.0 | 1.2 | .... |
| Nonprotein nitrogen | 11.1 | 11.3 | .... |
| Glucose | 5.6 | 6.6 | .... |
| Total | 17.7 | 19.1 | .... |
| Grand total | 318.4 | 319.4 | .... |
| Osmotic pressure (mM./L. equiv. NaCl) | 155.0 | 156.4 | .... |
| | Total Solids in Plasma, 7.2% | | |

* Average bicarbonate content determined separately in aqueous humor from 20 other eyes and 11 samples of plasma was 34.1 and 25.8 mM. per kilogram of water, respectively.
† Data from W. Heubner and R. Meyer-Bish (Über den Sulfatgehalt im Blutserum und Kammerwasser, Biochem. Ztschr. 126:184, 1926).
‡ Based on determinations performed on samples obtained from 13 other rabbits.

cally were found to be approximately equal. The chemical composition of both fluids is shown in the accompanying table.

The same worker formulated a concept of the dynamics of aqueous humor which he believes could account for the concentration of most of the constituents of this fluid relative to that of plasma, and also for the intraocular pressure of normal eyes and those having various pathologic conditions. This mechanism, as it relates to

32. Davson, H.: The Intra-Ocular Pressure and the Mechanism of Formation of the Intra-Ocular Fluid, Ophth. Lit. 4:3, 1950.
33. Kinsey, V. E.: A Unified Concept of Aqueous Humor Dynamics and the Maintenance of Intraocular Pressure, Arch. Ophth. 44:215 (Aug.) 1950.

the movement of constituents of the plasma into the posterior chamber, involves the production of unbalanced hydroxyl ions in the epithelium of the ciliary body, as suggested by Friedenwald,[34] and the simultaneous diffusion of all the constituents of the plasma into and out of the posterior chamber. The hydroxyl ions, by reaction with carbon dioxide, are converted to bicarbonate ions, which are electrically neutralized by sodium and other cations diffusing from the blood. The salts formed diffuse into the posterior chamber, thereby maintaining the aqueous humor hypertonic to the plasma. As a result of this hypertonicity, more water diffuses into the posterior chamber than diffuses out again; i. e., there is a net transfer of water into the posterior chamber. The excess transfer of water into the posterior chamber dilutes the other substances which are diffusing to and fro between the blood and the posterior chamber, so that, at steady state, most constituents exist in lower concentration in the aqueous humor than in the plasma. The aqueous humor thus "formed" flows between the iris and the lens into the anterior chamber, where there is a further exchange of nonelectrolytes, along with a major exchange of water across the iris. The electrolytes do not exchange, however, because the walls of the blood vessels of the iris are essentially impermeable to ions under normal conditions. All the constituents of the aqueous humor of the anterior chamber then escape by flow from the eye at the angle at a rate of about 3 microliters ($\mu$l) per minute. The influx of water as a result of hydrostatic and osmotic pressures, particularly the latter, is responsible for the intraocular pressure. The magnitude of the pressure depends on the rate of production of hydroxyl ions in the epithelium of the ciliary body, the ease of outflow at the angle, and, to a less extent, the permeability of the blood-aqueous barriers. Under normal conditions these factors are in balance. Under abnormal conditions they may vary independently and give rise to either an increase or a decrease in intraocular pressure.

Whereas the author believes that this theory can account for the mode of entrance and the relative concentration ratios (aqueous/plasma) of most of the constituents of the aqueous humor, special assumptions have to be made to account for the behavior of ascorbic acid.

A series of experiments designed to test the validity of Müller and Buschke's theory [35] of the mechanism of transfer of ascorbic acid into the eye was performed by Kinsey.[9] The theory under consideration postulated that ascorbic acid enters the posterior chamber from the plasma as its first oxidation product, i. e., as dehydroascorbic acid, to be reduced to ascorbic acid by the lens. It was a corollary of their thesis that ascorbic acid was unable to diffuse back out of the eye. The present studies showed that (1) the intact lens does not reduce dehydroascorbic acid in vitro; (2) injection of this acid into the posterior chamber of the eyes of living rabbits does not result in an increase of ascorbic acid in the anterior chamber; (3) the concentration of ascorbic acid is higher (1.4 times), rather than lower, in the posterior chamber than in the anterior chamber; (4) the concentration of dehydroascorbic acid in the aqueous humor does not increase after its intravenous injection; (5) the increase of ascorbic acid in the aqueous humor following intravenous injection of dehydroascorbic acid is not greater than could be accounted for by the increased concentration of ascorbic acid in the plasma.

34. Friedenwald, J. S.: The Formation of the Intraocular Fluid, Am. J. Ophth. **32**:9 (June, Pt. 2) 1949.

35. Müller, H. K., and Buschke, W.: Vitamin C in Linse, Kammerwasser und Blut bei normalen und pathologischem Linsenstoffwechsel, Arch. f. Augenh. **108**:368, 1934.

Langham [36] also observed an increase in the concentration of ascorbic acid in the aqueous humor following intravenous injection of dehydroascorbic acid and interpreted this as support of the Müller-Buschke theory. Langham, however, did not measure the concentration of ascorbic acid in the plasma after intravenous injection of dehydroascorbic acid, and hence apparently assumed that dehydroascorbic acid itself entered the posterior chamber, to be subsequently reduced to ascorbic acid by the lens. Actually, in one experiment, he observed an increase in the concentration of dehydroascorbic acid in the aqueous humor.

After injection of ascorbic acid and dehydroascorbic acid into rabbits with aphakic eyes, Langham observed less rise in the concentration of ascorbic acid in the aqueous humor and a greater rise in the amount of dehydroascorbic acid than was observed when the same experiment was performed in animals whose lenses were not removed. The results of the experiments he also interpreted as support of the Müller-Buschke theory.

The above observations, however, may indicate only that the blood-aqueous barriers in the eyes without lenses are more permeable to both acids; hence the ascorbic acid cannot build up to the high levels observed in the aqueous humor of normal eyes, and dehydroascorbic acid can diffuse into the aqueous humor in greater quantities than normal. In other words, there might be a leveling out of all constituents in the aqueous humor of aphakic eyes. Data of possible use in attempting to evaluate the alternative interpretations of Langham's work came from an experiment performed by me. With the aid of the late Dr. Buschke, I observed levels of ascorbic acid of the order of 70 mg. per 100 ml. in the aqueous humor of rabbit eyes sampled about one year after removal of the lenses when the eyes were definitely white and quiet. This observation, along with that indicating a higher concentration of ascorbic acid in the posterior chamber than in the anterior chamber, supports the general idea that the lens utilizes ascorbic acid, rather than synthesizes it from glucose, as has been suggested, or produces it by reduction of dehydroascorbic acid.

The concentration of ascorbic acid and dehydroascorbic acid in the aqueous humor of rabbit eyes is unaffected by atropine.[37]

Further studies by Scholz [38] indicate that the ratio of the concentration of sodium in the aqueous humor to that in the plasma of guinea pigs and monkeys is 1.025 and 0.87, respectively. The value of 0.87 in the monkey suggests that unless the sodium deficiency in the aqueous humor is made up by an excess of other cations the aqueous humor of this animal is hypotonic, and therefore unique among animals thus far investigated. The concentration of sodium in the aqueous humor was observed to be independent of lid closure.

The blood-aqueous barriers normally are permeable to cysteine and impermeable to cystine.[39]

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36. Langham, M.: The Transfer of L-Ascorbic Acid and Dehydro-L-Ascorbic Acid into the Aqueous Humour of the Rabbit and Cat, J. Physiol. **111**:388, 1950.

37. Cassady, J. V.; Thompson, J. M., and Pope, J. L.: Influence of Certain Mydriatics on the Ascorbic Acid Content of the Aqueous Humor, Arch. Ophth. **43**:813 (May) 1950.

38. Scholz, R. O.: Studies on the Physiology of the Eye Using Tracer Substances: III. Further Studies on the Steady-State Ratio of Sodium Between the Plasma and Aqueous Humor in the Guinea Pig and Monkey, Am. J. Ophth. **33**:420, 1950.

39. Niedermeier, S.: Blutkammerwasserschranke und Cystein, Klin. Monatsbl. Augenh. **116**:309, 1950; abstracted, Excerpta Med. XII **5**:7, 1951.

The rate of flow of aqueous humor was measured under elevated pressure in normal and glaucomatous eyes of human beings by Moses and Bruno,[40] using the electronic Schiøtz tonometer. At an average pressure of 31 mm. Hg the rate of flow was approximately 3 microliters (μl) per minute. The rate of outflow from glaucomatous eyes not operated on was, in general, low. Grant [41] refined the method by using longer periods of contact between the tonometer and the eye and took into account in his calculations not only the change in volume due to corneal indentation but also that due to scleral distention. This observer found that the rate of outflow varied from 2.3 to 5.4 μl per minute, with an average of 3.6 μl per minute. By the use of his method of calculation, it is possible to determine to what extent alterations of steady-state intraocular pressure are attributable to changes in resistance to outflow and to what extent to changes in net rate of aqueous humor formation. The rate of outflow of aqueous humor in human beings was also measured (Goldmann [42]) from the rate of loss of fluorescein from the eye. The author estimated the rate of outflow to be approximately 2 μl per minute.

Further information concerning the mechanism of outflow of aqueous humor is given by Weekers and Prijot [43] from experiments in which India ink was injected into the anterior chamber. They observed that the aqueous veins of rabbits do not carry aqueous humor when the intraocular pressure is less than 15 mm. Hg, and they also noted that with high intraocular pressures (40 to 50 mm. Hg) additional aqueous vessels are present.

The pressure in aqueous veins in the human eye was observed by Goldmann [44] to be 10 to 11 mm. Hg, while that in Schlemm's canal was slightly higher than 11 mm. Hg. Both pressures appear to be reduced by 2 to 3 mm. Hg in glaucoma simplex.

The relation between intraocular pressure and differences in osmotic pressure was well demonstrated again by Davson and Thomassen [45] and by Leydhecker.[46] The intraocular pressure was observed to fall upon continuous intravenous infusion of hypertonic saline solution in cats [45] and to rise in human beings after ingestion of water,[46] as done in the water-drinking test. Leydhecker made the important observation that the percentage of positive results in the water-drinking tests was as great in cases of chronic glaucoma as in cases of congestive glaucoma, and that the width of the chamber angle, as estimated gonioscopically, was unimportant. To the extent to which the drinking test gives a measure of resistance to outflow, as Leydhecker believes, these experiments demonstrate that flow is substantially independent of angle width.

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40. Moses, R. A., and Bruno, M.: The Rate of Outflow of Fluid from the Eye Under Increased Pressure, Am. J. Ophth. **33**:389, 1950.

41. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204 (Aug.) 1950.

42. Goldmann, H.: Über Fluorescein in der menschlichen Vorderkammer: Das Kammerwasser-Minutenvolumen des Menschen, Ophthalmologica **119**:65, 1950; abstracted, Ophth. Lit. **4**:17, 1950.

43. Weekers, R., and Prijot, E.: Recherches expérimentales sur les fonctions des veines aqueuses, Ophthalmologica **119**:321, 1950; abstracted, Ophth. Lit. **4**:100, 1950.

44. Goldmann, H.: Der Druck im Schlemmschen Kanal bei normalen Augen und bei Glaucoma Simplex, Experientia **6**:110, 1950; abstracted, Ophth. Lit. **4**:101, 1950.

45. Davson, H., and Thomassen, T. L.: The Effect of Intravenous Infusion of Hypertonic Saline on the Intra-Ocular Pressure, Brit. J. Ophth. **34**:355, 1950.

46. Leydhecker, W.: The Water-Drinking Test, Brit. J. Ophth. **34**:457, 1950.

LENS

The amino acid compositions of albuminoid, alpha- and beta-crystallin, and albumin of the bovine lens were determined by microbiologic methods,[47] and the amino-acid composition of the whole lens protein was determined by chromatographic analysis.[48]

Further information on the importance of a proper supply of amino acids for the maintenance of the normal lens is given by the interesting experiment of Schaeffer and Murray.[49] Young rats were fed a diet containing all the essential amino acids except tryptophan for 12 hours each day; during the following 12-hour period they were then fed another diet which contained tryptophan in the same amount as that employed in a control diet in which all the amino acids, including tryptophan, were present simultaneously. In the majority of the animals on the delayed-feeding diet corneal vascularization and cataract developed. This observation suggested to the authors that all essential amino acids must be present simultaneously for the lens to synthesize protein. The authors also noted that the tryptophan content of lenses of rats on diets lacking this amino acid is normal, indicating that "in diets deficient in essential amino acids, the protein synthesis is principally disturbed. Either the animal body can synthesize the protein characteristic for its body, or it cannot synthesize protein at all. It is not able to form a protein molecule from available inadequate building stones, in this case proteins deficient in tryptophan. Thus, in the proteins of lenses with tryptophan deficiency cataracts the tryptophan is in the same proportion as in the proteins of the normal lens. The inability to synthesize protein is evidenced by lack of growth."

Several aspects of the metabolism of the lens were investigated by Kinsey and Merriam. These authors[50] observed that rabbit lenses cultured in a medium of aqueous humor used approximately 3.5 mg. of glucose per day and produced approximately 2 mg. of lactic acid. They believe that the extra glucose is metabolized to carbon dioxide and water, as opposed to Ferrante,[51] who suggested that the difference in amount of glucose consumed and that converted to lactic acid might be utilized in the synthesis of ascorbic acid.

The same experimenters[52] showed that aminoacetic acid (glycine) labeled with $C^{14}$ was incorporated into glutathione of rabbit lenses cultured in a synthetic medium. The rate of incorporation indicated that glutathione is synthesized from its constituent amino acids at a rate of about 2.5% per hour—a rate sufficient to renew half of all the glutathione in the lens every 30 hours. It follows that this

47. Schaeffer, A. J., and Murray, J. D.: Amino Acid Composition of the Lens Proteins of the Bovine Eye, Arch. Ophth. **43**:1056 (June) 1950.

48. Merriam, F. C., and Kinsey, V. E.: Studies on the Crystalline Lens: III. Incorporation of Glycine and Serine in the Proteins of Lenses Cultured in Vitro, Arch. Ophth. **44**:651 (Nov.) 1950.

49. Schaeffer, A. J., and Murray, J. D.: Tryptophan Determination in Cataracts Due to Deficiency or Delayed Supplementation of Tryptophan, Arch. Ophth. **43**:202 (Feb.) 1950.

50. Merriam, F. C., and Kinsey, V. E.: Studies on the Crystalline Lens: I. Technic for in Vitro Culture of Crystalline Lenses and Observations on Metabolism of the Lens, Arch. Ophth. **43**:979 (June) 1950.

51. Ferrante, A.: Ricerche sulla glicolisi del cristallino, Ann. ottal. e. clin. ocul. **76**:209, 1950; abstracted, Excerpta Med. XII **5**:190, 1951.

52. Kinsey, V. E., and Merriam, F. C.: Studies on the Crystalline Lens: II. Synthesis of Glutathione in the Normal and Cataractous Rabbit Lens, Arch. Ophth. **44**:370 (Sept.) 1950.

compound is constantly being broken down at the same rate, since the concentration of glutathione remains essentially constant. These experiments indicate that the lens in situ is able to synthesize glutathione at a relatively rapid rate and would seem to dispose of the question of the source of supply of glutathione in the lens when repeated attempts have failed to demonstrate glutathione in the aqueous humor.

The rate of turnover of aminoacetic acid (glycine) in lens protein was also determined by these investigators [48] using glycine labeled with $C^{14}$. This amino acid was shown to be incorporated into protein at a rate of from 2.5 to 5% per day, and also to be rapidly converted to serine, an amino acid which, in turn, is incorporated into protein at a comparable rate.

Experiments by Bellows and Shoch,[53] in which alloxan was fed to rabbits, indicate that the concentration of glutathione in the lens decreases at approximately the time that the first opacities can be observed. It was noteworthy that if diabetes did not develop as a result of the alloxan, the concentration of glutathione did not decrease and cataract did not develop. This observation led the authors to conclude that the decreased glutathione concentration is caused by the diabetes, and not by the alloxan.

What appear to be diametrically opposite results were obtained by Waters,[54] who also injected alloxan into rabbits but observed that there was no significant decrease in the glutathione content of the lens, despite the fact that in half the animals bilateral cataract developed. The protein sulfhydryl content of the lens, however, decreased immediately after injection of alloxan and did not become normal for as long as two hours afterward. Waters also differs with Bellows in suggesting that alloxan itself may combine with some thiol group in the lens.

A high choline or vitamin-E content of diets containing no fats caused a significant delay in the appearance of cataract in rats as a result of alloxan injection.[55] The addition of liver fractions or vitamin A did not affect the time of appearance of cataract. Rats on a high fat diet did not have either glucosuria or cataract.

The inhibiting effect of cyanide on the oxygen uptake of the lens was observed by Ely and Robbie,[56] who suggested the possibility that cyanide may be acting on cytochrome. The authors were unable to isolate cytochrome from the lens, however, in sufficient quantities to assay spectrophotometrically. Their method was sufficiently sensitive to demonstrate cytochrome C if it were present in quantities in excess of 20 $\gamma$ per gram.

Incidental observations having chemical implication with regard to the lens were that there was an increase in the fluorescence of lenses of rats treated with naphthalene which was observable before any opacities could be seen [57] and that insufficient protein in the diet led to cataract formation.[58]

53. Bellows, J. G., and Shoch, D. E.: Alloxan Diabetes and the Lens, Am. J. Ophth. **33**:1555, 1950.

54. Waters, J. W.: Biochemical and Clinical Changes in the Rabbit Lens During Alloxan Diabetes, Biochem. J. **46**:575, 1950.

55. Charalampous, F. C., and Hegsted, D. M.: Effect of Age and Diet on Development of Cataracts in the Diabetic Rat, Am. J. Physiol. **161**:540, 1950.

56. Ely, L. O., and Robbie, W. A.: The Cyanide Sensitivity and Cytochrome-C Content of the Crystalline Lens, Am. J. Ophth. **33**:269, 1950.

57. Brolin, S. E.: Spectrophotometric Investigations on the Fluorescence of the Eye Lens in Rats Given Naphthalin, Acta ophth. **28**:163, 1950.

58. Morone, G.: Sul comportamento del cristallino in ratti sottoposti a diete ipoproteiche e iperlipidiche, Rass. ital. ottal. **19**:210, 1950; abstracted, Excerpta Med. XII **5**:178, 1951.

### RETINA

Because the oxygen consumption of the retina was substantially unaffected by poisoning with 0.001 N monoiodoacetic acid (which inhibits glycolysis), Auricchio [59] concluded that the retina is able to oxidize glucose in a direct manner. Since amino acids and fats may have been utilizing oxygen, the interesting possibility that a new pathway for oxidation of glucose, the initial steps of which do not go through ordinary glycolytic stages, may be operative in the retina will require confirmation.

The observation that light-adapted retinas contain more creatine, and dark-adapted retinas more phosphocreatine, suggests to Hwang [60] that visual purple and phosphocreatine breakdown are associated, as are also visual purple regeneration and phosphocreatine synthesis. In contrast to early experiments,[61] no difference in the oxygen uptake in retinas in a dark-adapted state or difference in the oxygen uptake in retinas in a dark- or a light-adapted state was observed.[62]

The maintenance of high potassium concentration in the retina, and incidentally also in the brain, is dependent upon the simultaneous presence of both glucose and glutamate.[63] Glucose apparently provides the energy for potassium transport into these tissues against a concentration gradient; it can be replaced by lactate or pyruvate. The role of glutamate is not fully understood.

The contents of ribonucleic acid in dark- and in light-adapted retinas were the same.[64] This observation is contrary to previous ones made on cells from cortical centers which underwent physiologic stimulation.

Denton, Pirenne, and Hartridge [65] criticized the theory of Dartnall and Thomson [66] in which macular yellow is considered to play a part in the oxidation-reduction system carrying oxygen to those parts of the fovea not supplied with capillaries.

### PHOTOCHEMISTRY

SECTION WRITTEN BY RUTH HUBBARD, PH.D., BIOLOGICAL LABORATORIES, HARVARD UNIVERSITY, CAMBRIDGE, MASS.

The original contributions in this field fall into two main groups: (1) those dealing with the retinenes and vitamins A, the carotenoids which are the precursors, as well as the products, of bleaching of rhodopsin and porphyropsin, and (2) those concerned with the chemistry or photochemistry of the visual pigments themselves.

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59. Auricchio, G.: Sull'ossidazione diretta del glucosio da parte della retina, Ann. ottal. e clin. ocul. **76**:52, 1950; abstracted, Excerpta Med. XII **4**:542, 1950.

60. Hwang, T. F.: Creatine in Dark and Illuminated Retinae, Japan. J. Physiol. **1**:160, 1950; abstracted, Ophth. Lit. **4**:500, 1951.

61. Dickens, F., and Greville, G. D.: Metabolism of Normal and Tumour Tissue: IX. Ammonia and Urea Formation, Biochem. J. **27**:1123, 1933.

62. Hwang, T. F.: Respiration of Retinal Tissue, Japan. J. Physiol. **1**:169, 1950.

63. Terner, C.; Eggleston, L. V., and Krebs, H. A.: Role of Glutamic Acid in Transport of Potassium in Brain and Retina, Biochem. J. **47**:137, 1950.

64. Ehrlich, G., and Dische, Z.: Content of Desoxyribo and Ribonucleic Acids of Retina Under Various Conditions, Proc. Soc. Exper. Biol. & Med. **74**:40, 1950.

65. Denton, E. J.; Pirenne, M. H., and Hartridge, H.: Retinal Oxygen Supply and Macular Pigmentation, Nature, London **165**:304, 1950.

66. Dartnall, H. J. A., and Thomson, L. C.: Retinal Oxygen Supply and Macular Pigmentation, Nature, London **165**:876, 1949.

*The Retinenes and Vitamins A.*—Wald [67] elaborated and summarized earlier work on the interconversion of the retinenes and vitamins A. Both vitamin $A_1$ and vitamin $A_2$ can be oxidized on manganese dioxide to the corresponding retinene, although the ratios of manganese dioxide to vitamin A differ in the two cases. The enzymatic reduction of either retinene can be performed by an enzyme system found in frog or cattle (rhodopsin system: retinene$_1$ and vitamin $A_1$), as well as in fresh-water fish (porphyropsin system: retinene$_2$ and vitamin $A_2$). It consists of an apoenzyme, retinene reductase, and reduced coenzyme I, or cozymase ($DPN\text{-}H_2$). It was also shown that the fat-soluble retinenes can be brought into aqueous solution by aqueous retinal extracts containing retinene reductase or other proteins. This confirms the earlier studies of Ball and co-workers,[68] who showed that retinene$_1$ readily combines with proteins or amino acids, thereby becoming a pH indicator. (These retinene-amino complexes presumably constitute what Lythgoe has called "indicator yellow." [69])

Bliss [70] showed that alcohol dehydrogenase obtained from horse liver reversibly oxidizes vitamin $A_1$ to retinene$_1$ in the presence of coenzyme I. He determined the equilibrium constant of the vitamin $A_1$-retinene$_1$ system (0.033 at pH 7.0) and found that it varied linearly with the pH in a manner similar to the equilibrium constant of the ethyl alcohol-acetaldehyde system.[71]

*The Visual Pigments.*—Various aspects of the bleaching rhodopsin were studied. The bleaching of rhodopsin was analyzed into a light reaction and a series of "dark" (slow thermal) reactions by Wald and co-workers.[72] The light reaction was demonstrated by allowing light to act on rhodopsin in a glycerin-water "glass" at —30 to —100 C. or in a dry gelatin film. In either case, light shifts the absorption spectrum about 5 mμ toward shorter wave lengths and produces a 5 to 10% increase in extinction. (A slight fall in extinction was noted with vitrified-frog rhodopsin.) The new substance thus formed was called "lumi-rhodopsin." At temperatures above —20 C. it is unstable and is transformed into meta-rhodopsin, a substance characterized by an absorption maximum 5 to 10 mμ further toward the blue. Meta-rhodopsin is stable in the absence of water and relatively stable at low temperatures. In the presence of water, meta-rhodopsin goes over in the dark to a mixture of regenerated rhodopsin and retinene$_1$ + protein in roughly equal amounts. The authors suggest that the excitation of vision is probably due to the step rhodopsin to lumi-rhodopsin or some reaction which bears a close temporal relation to it, such as the transformation of lumi-

67. Wald, G.: The Interconversion of the Retinenes and Vitamin A in Vitro, Biochim. et biophys. acta **4**:215, 1950.

68. Ball, S.; Collins, F. D.; Morton, R. A., and Stubbs, A. L.: Chemistry of Visual Processes, Nature, London **161**:424, 1948. Ball, S.; Collins, F. D.; Dalvi, P. D., and Morton, R. A.: Studies in Vitamin A.: XI. Reaction of Retinene$_1$ with Amino Compounds, Biochem. J. **45**:304, 1949.

69. Lythgoe, R. J.: Absorption Spectra of Visual Purple and of Indicator Yellow, J. Physiol. **89**:331, 1937.

70. Bliss, A. F.: Action of Alcohol Dehydrogenase on Vitamin A, Biol. Bull. **99**:330, 1950.

71. Racker, E.: Crystalline Alcohol Dehydrogenase from Bakers' Yeast, J. Biol. Chem. **184**:313, 1950.

72. Wald, G.; Durell, J., and St. George, R. C. C.: The Light Reaction in the Bleaching of Rhodopsin, Science **111**:179, 1950.

rhodopsin to meta-rhodopsin. The spectrums of both lumi-rhodopsin and meta-rhodopsin are invariant with the pH and may therefore be taken to constitute components of Lythgoe's "transient orange." [73]

Collins and Morton [74] have studied rhodopsin and the first products of its bleaching. They discuss various methods of extraction of rhodopsin and the purity of the rhodopsin yielded by each and conclude that the best preparations are obtained from isolated rod outer limbs which have been floated out by differential centrifugation in 45% sucrose, according to Saito's method.[75] The rod outer limbs are subsequently hardened in alum and extracted with digitonin. Their best solutions are similar in their absorption characteristics to those reported by Wald,[76] but the maximum extinction of the protein band at 270 mμ, however, is variable and higher than that reported by Wald for his best preparations. Collins and Morton believe that their solutions contain varying amounts of protein contaminants, as well as melanin and phospholipids.

Collins and Morton also present experiments and calculations bearing on the constitution of "indicator yellow" and "transient orange" and try to assign structural formulas to the carotenoid prosthetic groups of these two hypothetical substances, as well as to the prosthetic group of rhodopsin. Wald [76] had suggested that the rhodopsin chromophore contains two molecules of retinene$_1$. Collins and Morton believe that the prosthetic group of all three forms consists of two molecules of retinene$_1$ joined through an amino group on the protein. In their conception, the bleaching of rhodopsin consists first of the formation of a free radical ("transient orange"), which dismutates to yield equal amounts of slightly altered rhodopsin ("isorhodopsin") and the acid form of "indicator yellow." This theory, although ingenious, is still highly speculative, since no conclusive evidence exists that the prosthetic group of rhodopsin in fact contains two molecules of retinene$_1$ or that amino groups are involved in its formation.

A number of abstracts have appeared on the visual pigments and their bleaching reactions. Dartnall [77] published a color photograph of rhodopsin which confirms objectively the subjective impression of all previous workers in the field that it is red. He also claims to have discovered two or three cone photosensitive pigments in the tench retina and, through a few simple computations, predicts the

73. Lythgoe, R. J., and Quilliam, J. P.: Relation of Transient Orange to Visual Purple and Indicator Yellow, J. Physiol. **94**:399, 1938.

74. Collins, F. D., and Morton, R. A.: Studies on Rhodopsin: 1. Methods of Extraction and the Absorption Spectrum, Biochem. J. **47**:3, 1950; 2. Indicator Yellow, ibid. **47**:10, 1950; 3. Rhodopsin and Transient Orange, ibid. **47**:18, 1950.

75. Saito, Z.: Isolierung der Stäbchenaussenglieder und spektrale Untersuchung des daraus hergestellten Sehpurpurextraktes, Tohoku J. Exper. Med. **32**:432, 1938.

76. Wald, G.: The Photochemistry of Vision, Docum. ophth. **3**:94, 1949.

77. Dartnall, H. J. A.: Colour Photography of Visual Purple Solutions, Brit. J. Ophth. **34**:447, 1950.

existence of three more.[78] Serious doubt, however, has recently been cast on his experiments and calculations by Collins and Morton.[79]

A group of workers in France reported that "transient orange," prepared in red light, is not as transient as has been believed heretofore.[80] The spectrum of stable "transient orange" is, however, admirably mimicked by a recent spectrum by Collins and Morton [79] of a 10% residue of unbleached rhodopsin in the presence of its bleached product. The possibility that the "transient orange" of Berger and Segal is, in fact, a residue of unbleached rhodopsin would also explain Segal's startling claim that "transient orange" is photosensitive.[81]

Crozier [82] presented a large series of measurements of the spectral sensitivity of the human fovea, carried out on a single eye of one observer. His results differ from all comparable measurements previously reported in displaying a considerable number of maximums and minimums closely spaced throughout the spectrum. Crozier assigns the principal importance, not to the measurements of spectral sensitivity, but to their standard deviations, which also display periodic maximums and minimums throughout the spectrum. These Crozier believes to represent the absorption bands of certain respiratory enzymes, which he assumes to be present in the foveal cones and which, in addition to their enzymatic function, sensitize the cones to light. Thus he ascribes individual maximums to cytochrome C reductase, reduced cytochrome A and cytochrome C, and oxidized cytochrome C. It is not made clear how the cones are to achieve the differential sensitivities required for color vision by the use of such respiratory enzymes, which presumably are present in all the cells. It should be noted also that cytochrome C reductase is an enzyme obtained from yeast, not yet identified in any animal tissue, and that, of the bands of the cytochromes, the most prominent Soret bands in the violet seem to make no appearance in Crozier's data.

Several communications appeared concerning the regeneration of rhodopsin from retinene$_1$ and from vitamin A$_1$.[83] Wald and Brown showed that solutions of bleached rhodopsin regenerate up to 85% of their original rhodopsin content if they are incubated in the dark in the presence of an excess of retinene$_1$.[83a] Good regeneration was also observed when purified rhodopsin protein, extracted from bleached retinas, was allowed to react with retinene$_1$ in aqueous digitonin. When frog rhodopsin protein was mixed with retinene$_2$, a photosensitive pigment was

78. Dartnall, H. J. A.: New Photosensitive Pigments from Tench Retina, Nature, London **166**:207, 1950; Action of the Scotopic Pigments of the Rod Cell, in Abstracts of 18th International Physiological Congress, Copenhagen, 1950, p. 25.

79. Collins, F. D., and Morton, R. A.: Retinal Receptors, Nature, London **167**:673, 1951.

80. Berger, P., and Segal, J.: Le spectre d'absorption de l'orangé transitoire rétinien, Compt. rend. Soc. biol. **144**:478, 1950.

81. Segal, J.: La photolyse de l'orangé transitoire rétinien, Compt. rend. Soc. biol. **144**:403, 1950.

82. Crozier, W. J.: On the Visibility of Radiation at the Human Fovea, J. Gen. Physiol. **34**:87, 1950.

83. (*a*) Wald, G., and Brown, P. K.: Synthesis of Rhodopsin from Retinene$_1$, Proc. Nat. Acad. Sc. **36**:84, 1950; (*b*) Synthesis of Rhodopsin from Retinene$_1$, in Abstracts of 18th International Congress, Copenhagen, 1950, p. 499. (*c*) Wald, G., and Hubbard, R.: The Synthesis of Rhodopsin from Vitamin A$_1$, Proc. Nat. Acad. Sc. **36**:92, 1950. (*d*) Hubbard, R., and Wald, G.: Synthesis of Rhodopsin from Vitamin A$_1$, in Abstracts of 18th International Physiological Congress, Copenhagen, 1950, p. 264.

formed, with its "difference spectrum" (difference in absorption spectrum before and after bleaching) displaced 15 mμ toward the red, i. e., intermediate in spectrum between rhodopsin and porphyropsin. The synthesis of rhodopsin was inhibited by formaldehyde, owing to a competition for reactive groups on rhodopsin protein, and by hydroxylamine, which "traps" retinene$_1$ by condensing with it to form the oxime. The authors believe the condensation of retinene$_1$ and rhodopsin protein (opsin) to be a spontaneous reaction which occurs without the participation of any other molecules. The pH optimum for the regeneration of cattle rhodopsin lies at 5.7 to 6.3, depending on the buffer anion used.[83b]

Bliss [84] published a note in which he reported that a water-soluble, heat-labile factor from the pigment epithelium aids in the regeneration of rhodopsin in bleached solutions.

The regeneration of rhodopsin from vitamin A$_1$ was studied in retinal homogenates and in aqueous digitonin extracts of retinas.[85] Since the time of Kühne it has been believed that this process does not occur in the isolated retina and requires the cooperation of the pigment epithelium.[86] Wald and Hubbard [83c] were able to show that bleached isolated retinas or retinal homogenates in the dark do, in fact, synthesize about 10% of their potential rhodopsin content. This yield is doubled to 20% by supplementation with excess diphosphopyridinenucleotide (DPN). It is doubled also by the addition of a homogenate of the pigment layers of the eye—choroid and pigment epithelium. These two effects are additive, so that retinal homogenates incubated in the presence of both DPN and pigment-layer homogenate regenerate about 40%. A 10% regeneration was observed also in aqueous digitonin extracts of the retina supplemented with vitamin A$_1$ and DPN. The following is suggested as a possible mechanism of this reaction: It was shown previously that retinas contain an enzyme system (retinene reductase) capable of reducing retinene$_1$ to vitamin A$_1$ in the presence of reduced DPN.[87] In the present study this reaction was shown to be reversible. The equilibrium of the reaction is far toward the side of the reduction of retinene$_1$. In the presence of excess DPN and hydroxylamine, however, bleached retinal homogenates oxidized about 50% of their vitamin A$_1$ to retinene$_1$ in the course of two hours. Hydroxylamine traps retinene$_1$ by forming the oxime and thereby displaces the equilibrium. It is postulated that the spontaneous condensation of retinene$_1$ and rhodopsin protein (opsin)[81a, b] might constitute a comparable trapping mechanism and thus drive the oxidation of vitamin A$_1$ to retinene$_1$ via the retinene-reductase system. The pigment epithelium probably acts on the same system, possibly by supplying vitamin A$_1$ or respiratory factors to keep DPN oxidized. In summary,

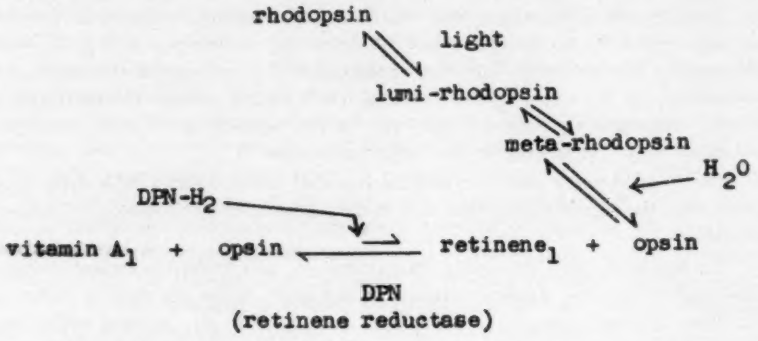
84. Bliss, A. F.: Pigment Layer Factor in Visual Purple Regeneration, Federation Proc. **9**:12, 1950.

85. Wald and Hubbard.[83c] Hubbard and Wald.[83d]

86. Kühne, W.: Chemische Vorgänge in der Netzhaut, in Hermann, L.: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, 1879, Vol. 3, Pt. 1, p. 317.

87. Wald.[67] Wald, G., and Hubbard, R.: The Reduction of Retinene$_1$ to Vitamin A$_1$ in Vitro, J. Gen. Physiol. **32**:367, 1949.

it is suggested that all the phenomena so far observed can be explained on the basis of a reformulation of the visual cycle as a system of coupled equilibriums [84]:




The intermediate stages in the bleaching of rhodopsin may not all be retraced in its synthesis from retinene$_1$ and opsin.

Reviews of the literature for 1949 have appeared in this journal [88] as well as in *Physiological Reviews*.[89] Tansley has written a review devoted entirely to visual purple which covers the literature through 1948.[90]

Kresge Eye Institute.

88. Kinsey, V. E.: Physiologic Chemistry of the Eye, Arch. Ophth. **44**:584 (Oct.) 1950.
89. Granit, R.: Physiology of Vision, Ann. Rev. Physiol. **12**:485, 1950.
90. Tansley, K.: Visual Purple, Docum. ophth. **4**:116, 1950.

# Society Transactions

## COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Wilfred Fry, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

*Dec. 21, 1950*

**Intermittent Ophthalmoplegia Due to Angioneurotic Edema.** Dr. Wilfred E. Fry and (by invitation) Dr. Nathan Schlezinger.

A woman aged 25 had episodic pareses of the extraocular muscles, associated at times with palpebral edema, the attacks recurring in an irregular and unpredictable manner. Frequent direct observations on this patient extended over a period of about six months, with therapy relatively ineffective in controlling the intermittent ophthalmoplegia. A survey of the literature indicates that intermittent ophthalmoplegia is a rare ocular manifestation of angioneurotic edema, although involvement of the nervous system and of the eye otherwise is well recognized. A consideration of the differential diagnosis includes a number of ailments which may produce intermittent ophthalmoplegia, such as intracranial aneurysm, ophthalmoplegic migraine, myasthenia gravis, and cyclic oculomotor nerve paralysis.

### DISCUSSION

Dr. William E. Krewson III: Intermittent, or variable, ophthalmoplegia is unusual, and when attributable to angioneurotic edema is rare. The authors are fortunate to have seen such an interesting case and to have been able to follow the patient over so long a period.

Angioneurotic edema is not a clear-cut disease entity but, rather, a symptom complex, which is little understood. It is manifested by an allergic disturbance (not necessarily immediate) in the dermis, similar to urticaria, and is accompanied by large areas of edema, which involve the subcutaneous and deep structures. Often a hereditary history of allergy is obtained, and the condition usually responds, at least in some degree, to epinephrine and antihistamine therapy. The case that was presented probably falls into this category.

To the full discussion of differential diagnosis by the essayists I might add the remote possibility of trichinosis; however, they did mention dermatomyositis, the synonym of which is pseudotrichinosis. Aside from angioneurotic edema, the most likely possibilities in this case are myasthenia gravis, intracranial aneurysm, cyclic ophthalmoplegia, and atypical ophthalmoplegic migraine, and all these conditions apparently have been ruled out.

Determination of the muscles involved in cases of multiple oculomotor paralyses may be exceedingly difficult, and when the paralysis is too transient and rapidly variable as in this case accurate diagnosis is well-nigh impossible. Edema of the meninges has been thought to cause stretching or compression of the cranial nerves as they pass over the blood vessels or other anatomic structures within the cranium; but, as the authors have stated, the great and rapid variability of the ophthalmoplegia in their case leads to the conclusion that the disturbance was located peripherally. Although the neuromuscular mechanism may have been involved directly, it is easy to conceive of the swollen orbital contents interfering mechanically with the action of the muscles, the muscles themselves being compressed or their integrity actually invaded by edematous fluid.

This beautiful presentation teaches that allergy must be added to the ever-increasing list of diagnostic possibilities which are to be considered when one is confronted with a case of oculomotor paralysis.

**Exposed Implants: A Follow-Up Report.** Dr. Patrick J. Kennedy and Dr. James S. Shipman.

In March, 1949, we reported on a series of 45 ocular enucleations or eviscerations. Of these, 10 were simple enucleations. In 18 cases a buried implant was placed in the socket. These implants are still in place. In 17 cases an exposed implant was used. Of these, three had been extruded before our original presentation. Since then, three more have been extruded, making a total loss of six, or 36%. Since 1949, 10 exposed implants have been used. Four of these were extruded in three to 15 mo., making a loss of 40%. Thus, of 27 exposed implants, 10 have been extruded, a total of 37%.

In these cases the primary results were excellent. After a few months a thick, viscid, mucoid secretion began coming from the socket. This was usually preceded by a partial exposure of the implant. This secretion was frequently accompanied by a foul odor. Neither the secretion nor the odor responded very well to antiseptic and antibiotic therapy.

We believe that the tantalum mesh, while serving as the anchor for the tissues on the implant, is the site of this secondary infection, which is very hard to eradicate.

The incidence of extrusion—practically 1 in 3—is so high that we do not feel justified in continuing the use of the exposed implant until we have a better method of controlling the secondary infection, which apparently plays such a large part in initiating the extrusion.

DISCUSSION

Dr. James S. Shipman: Two years ago, when Dr. Kennedy's interest in implants became manifest I gave him permission to take over all the enucleations on our service at the Wills Hospital and to do the operation that he thought was best. He has had a fair opportunity to perform many enucleations and to try out the various types of implants. Fortunately, or unfortunately, in recent years, owing to good surgery or good fortune, we have not had enough enucleations on the service to build up our statistics. As a matter of fact, the few enucleations that we have done seem to show the same good results that the early statistics did, and I think that eventually Dr. Kennedy will work out an implant that will be a great improvement over any in present use.

As I stated almost two years ago, when Dr. Kennedy presented this subject the first time, I felt almost the same about these implants as did one of our patients, who came in with an eye full of mucus and smelling bad, saying, "Doctor, this thing stinks." I still think that most of them do. In my opinion, the theory of the exposed implant is wrong, and it will not work out in practice. I believe that the implant must be covered or buried in order to stay in and give the movement that it should. Certainly, in theory one should get more motion from an exposed implant that is directly connected to the prosthesis, but I do not believe that in years to come many of these implants will remain in. Certainly, the few that I have used myself have been very unsatisfactory and have caused me a great deal of concern.

I believe that the Dimitry implant in the scleral cup is the ideal type for use after enucleation when it is not contraindicated by such conditions as tumor of the globe or orbit or a virulent infection. I have a few cases of 15- or 20-years' duration in which a movable socket with a shell prosthesis lies right over a gold sphere in the scleral cup. In one case the gold sphere has been in for 21 years. The result is as good as I have ever seen, regardless of whether the implant was exposed or buried. Logically, one would expect to get better motion when the muscles are not disturbed. Dr. Kennedy, at a meeting of this section, pointed out that an implant which was flatter anteroposteriorly and wider in the lateral diameter

offered a better chance for getting free motion of the prosthesis. He and I have talked about this, and he is to develop an implant to go inside the scleral cup, somewhat on the order of the Allen implant, and shaped very much like a curling ball. The only thing I do not like about the Allen implant procedure is the cutting of the muscles and bringing them forward through a ring and suturing them. It is only natural that they will gradually slough off and be lost, and the implant will turn to one side or the other.

The final solution to this problem is an implant similar to the Allen implant, but buried in the scleral cup, and completely covered, possibly with a magnet in the center of it. At present we do not have the answer, but give Dr. Kennedy another two years, and I think he will have it.

**Causes of Failure in Retinal-Detachment Surgery.** DR. P. ROBB MCDONALD.

An analysis of 88 cases of retinal detachment treated surgically by the author revealed 24 failures. He classified causes of failure as those occurring in the preoperative period, those in the operative period, and those in the postoperative period. The most important factor would appear to be finding the break in the retina. Tears were found in 86% of the successful cases and in 33% of the unsuccessful cases. Other causes of failure were tears involving more than one quadrant of the retina, two cases; retinal folds and vitreous contraction, seven cases; intraocular foreign bodies, three cases; myopia of —20 D. or greater, two cases; active uveitis, one case, and metastatic carcinoma of the choroid, one case.

Operative causes of failure were listed as failure to close the break, insufficient diathermy, excessive diathermy, insufficient drainage of the subretinal fluid, and hemorrhage.

Postoperative causes of failure were listed as iridocyclitis, hemorrhage, and contraction of the vitreous. Probably more than one factor plays a part. Certain factors, such as contraction or separation of the vitreous, are beyond the control of the ophthalmologist, but the number of failures will be appreciably reduced if the ophthalmologist is willing to spend the time in a careful preoperative examination and meticulous ophthalmoscopic observation during the operative procedure.

DISCUSSION

DR. JAMES S. SHIPMAN: Dr. McDonald has given us something to think about; we often derive more good from discussing our failures than from presenting our successes. Dr. McDonald has presented this picture well and concisely and has pointed out why we have failed, when many times we have wondered. As he stated, retinal-detachment surgery tests the perseverance, the skill, and the ingenuity of the surgeon.

There are not many points in Dr. McDonald's paper with which I can disagree. There are some I should like to emphasize, but time will not allow. I should like to note a few points which he did not have time to cover. First, he gave as a reason for the increased number of cases of retinal detachment the increased longevity of the patients whom we are seeing. I think that is true, but there is another important reason, namely, that not only the ophthalmologist, but the general physician, as well, is becoming more retinal-detachment-minded and has come to know that there is something to do for retinal detachments, which many years ago he did not know; and he sends the patients to eye centers or to specialists who are doing retinal-detachment surgery.

To Dr. McDonald's three types of failure I should like to add a fourth—failures for which we cannot account.

With regard to the preoperative factors, Dr. McDonald has brought out the most important point, one which has been emphasized by many, namely, that the cause of retinal detachment is a tear in the retina and the only way to cure the detachment is to seal off this tear. Indeed, careful preoperative study, with a diligent

search for the tear in the retina, is one of the most important factors in successful retinal-detachment surgery.

I do not entirely agree that Scheppen's method of indirect ophthalmoscopy offers a great deal more than careful direct ophthalmoscopy. In fact, I think that the latter is much more important. Certainly, fixed folds of the retina, as emphasized by Scheppens, always suggest a poor prognosis, as does failure of the retina to settle back near its proper position after the patient has been put to bed in a position favorable for this. Arruga has pointed out that large tears which allow the vitreous to come in contact with the choroid for any length of time always offer a poor prognosis, since the choroid becomes atrophic and cannot be coagulated easily, and the coagulation has to be placed much farther back than one would expect.

I was glad to hear of Dr. McDonald's results in aphakia, which parallel those of my own very closely. I feel that aphakic eyes, which are otherwise healthy, do not carry a much worse prognosis than do phakic eyes, provided a secondary capsule does not interfere with a good view of the fundus. The chief reason for poor results in aphakic eyes is the loss of an unusual amount of vitreous at the time of cataract extraction, postoperative hemorrhage with subsequent organization and contraction, or possibly a low-grade endophthalmitis. Barring these three complications, I think that aphakia offers a favorable prognosis in 50% of cases.

Another reason for poor central vision following operation for retinal detachment is involvement of the macula by the detachment. However, children and young adults seem to tolerate such a detachment for a longer period than older adults and the aged do. Reese has pointed out a type of cystic degeneration which frequently follows detachment involving the macular region.

Too much diathermy is likely to give rise to a virulent postoperative iridocyclitis with hemorrhage in the anterior chamber, and sometimes massive vitreal hemorrhage with extensive organization and contraction of the vitreous. A posterior cortical cataract consisting of many "bubbles," suggesting soapsuds, may be present. I have seen this in at least 25 young adults with no such opacities in the fellow eye.

Finally, another reason for failure is allowing the patient too many liberties too early. The surgeon doing retinal-detachment surgery should have a definite routine, and this should be followed religiously for a considerable length of time after the patient has left the hospital.

I can think of many more reasons for failures than Dr. McDonald has mentioned, possibly because I have had more failures than he has. However, time will not allow me to mention more.

I want to thank Dr. McDonald for this interesting and informative paper, and I feel that his incidence of only 24 failures among 88 operations is better than the average, particularly in view of the type of cases in which he operated. Many of them, I happen to know, were cases that most ophthalmologists would have turned down, thinking that the condition was hopeless.

Dr. Edmund B. Spaeth: Failures in retinal-separation surgery are not like those in other surgical procedures, in which the manual dexterity of the operator and the completeness with which the procedure is carried out are very important. There are many other factors responsible for failures. As a matter of fact, at a symposium on retinal separation, at the International Congress in London in 1950, the acclaimed consensus was that retinal separation cannot be operated on successfully unless one takes into consideration three, and probably four, distinct entities, for one technique will answer only one set of conditions. The techniques are surface diathermy, transscleral diathermy, and scleral resection. As to the fourth, there are definite indications for scleral trephining with chemical cauterization. Each operation has a primary indication. A scleral resection should not be resorted to as a final, frenzied procedure, after three or four other measures have been unsuccessful.

There is no doubt that aphakia and the retinal separations of aphakia are connected with uveitis. In a paper presented five years ago before the American Academy of Ophthalmology and Otolaryngology the triad of uveitis, cataract, and retinal separation was noted (*Tr. Am. Acad. Ophth.* [1944] **49**:265 [May-June] 1945). The retinal separation of aphakia may, in addition, be due to the anatomic situation present from the loss of the supporting diaphragm to the vitreous, i. e., the suspensory ligament and lens.

There is no doubt that the essentials in the preoperative status are retinal holes, the state of the vitreous, and the degree of the myopia and that those three factors are by far the most important thing except, of course, for the perforating injuries which result in traumatic separations. The two essentials for surgical success are the closure of all retinal lacerations and the provision for subretinal drainage, it being the drainage of the fluid through the retinal holes that is responsible for the separation. As long as those are the two operative requirements, they must be adjusted to the indications present.

High myopia with detachment does not lend itself well to extensive transscleral diathermy. The retinal separation of aphakia in the presence of a fluid vitreous lends itself best to a scleral trephining with chemical cauterizations. In cases with considerable vitreous contraction the prognosis is very poor, regardless of the technique used.

For the retinal separation of retinal and choroidal coloboma a scleral resection should be the primary procedure. Flat retinal separations are best handled by surface scleral diathermy. Retinal lacerations without separation must be operated on, and in management of these the only point of significance is the closure of the retinal hole. There is no need to arrange for subretinal drainage.

## ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

**Kenneth C. Swan, M.D., *Chairman***

**James H. Allen, M.D., *Secretary***

**and**

## AMERICAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

**Robert J. Masters, M.D., *Chairman***

**Trygve Gundersen, M.D., *Secretary***

***Combined Meeting, June 13-15, 1951***

A combined meeting of the Association for Research in Ophthalmology, Inc., and the Section on Ophthalmology of the American Medical Association was arranged by the officers of the societies to meet in Atlantic City, N. J., at the One-Hundredth Annual Session of the American Medical Association. Heretofore, the Association for Research in Ophthalmology has met a few days prior to the Section on Ophthalmology, and the programs have not been correlated. The arrangement carried out this year, for the first time, was so satisfactory that in all probability the two meetings will be held next year as they were this year.

On Wednesday and Thursday forenoons, June 13 and 14, the meetings were in charge of the Association for Research in Ophthalmology, with Dr. Kenneth C. Swan, of Portland, Ore., as chairman, and Dr. James H. Allen, of New Orleans, as secretary.

A study of aqueous veins of patients wearing various types of contact lenses revealed a reversal of flow of the aqueous, an increase in the red blood cell content, cyanosis, occasional sludging, and stagnation in the part covered by the rim of the contact lens. These changes cannot explain phenomena interfering with tolerance of contact lenses, but at least they indicate an unphysiologic situation. Dr. K. W.

Ascher, of Cincinnati, who read the paper, recently has completed a book on aqueous veins, which probably will be published within a few months.

Dr. Gordon S. Christiansen, of Iowa City, reported experiments on lens metabolism, based on observed oxygen consumption of the lens. His experiments indicated that what has generally been referred to as "respiration" is thermostable and therefore cannot be a true enzymatic respiratory reaction. The exact nature of this gaseous exchange is not completely known, but evidence is presented that it involves the production and release of carbon dioxide as well as the utilization of oxygen.

The influence of adrenalectomy on the rate of flow of the aqueous humor in rabbits was determined by Dr. Jonas S. Friedenwald, of Baltimore, and Dr. V. Everett Kinsey, of Detroit, on the basis of the increase in ascorbic-acid concentration in the aqueous following large intravenous injections of ascorbic acid. Application of this method to normal and adrenalectomized rabbits revealed that the turnover rate for aqueous after adrenalectomy was approximately 30% slower than in normal animals. By a somewhat similar method, Dr. Peter C. Kronfeld, of Chicago, was able to demonstrate the transconjunctival passage of aqueous in eyes that had been trephined for glaucoma.

In a study of the electroencephalographic changes in 77 children in the motility clinic of the Illinois Eye and Ear Infirmary, Dr. M. L. Stillerman and Dr. E. L. Gibbs, of Chicago, reported that minor occipital changes were detected in 10%. No correlation could be obtained between amblyopia, fusion, or retinal correspondence and any changes in the electroencephalogram.

Dr. John W. Patterson, of Cleveland, reported on the occurrence of cataract in diabetic rats. It was found that a minimum time of 5.2 weeks and a minimum blood sugar level of 225 mg. per 100 cc. was required for the formation of diabetic cataract. It was thought that there might be loss through the kidney of an essential metabolite that competes with glucose for reabsorption. Thus, a deficiency might develop, with resultant cataract formation. Phosphate is lost excessively in uncontrolled diabetes as a result of competition with glucose for reabsorption in the kidney. This loss of phosphate in the kidney may produce changes in the lens similar to those that occur with parathyroid deficiency and thus cause cataract.

The viability of retinal cells following deprivation of blood supply was studied by Drs. C. G. Smith and C. D. Baird, of Toronto, Canada. The ischemia of the retina was produced in some rats by cutting the retinal and ciliary vessels and in others by raising the intraocular pressure sufficiently to produce collapse of the retinal vessels. The results of the two experimental procedures were similar, and histologic changes appeared within 15 to 20 minutes after the onset of ischemia. The bipolar cells showed the most conspicuous changes and appeared to be the first to be injured. In the experiment in which the ischemia was produced by raising the intraocular pressure, some of the animals were allowed to survive after the treatment, and a study of these revealed that if the ischemia did not last more than 10 minutes the retina had a normal appearance after 21 days. However, if the ischemia lasted 20 minutes, the bipolar cells and most of the ganglion cells had disappeared after 20 days. Longer periods of anemia led to complete degeneration of the retina.

The program of the Section on Ophthalmology was given on Thursday and Friday afternoons.

Dr. W. Morton Grant, of Boston, reported on "Clinical Measurements of Aqueous Outflow." Measurements made on several hundred eyes of patients and normal volunteers appeared to have established that an abnormal resistance to the escape of aqueous humor is the rule in glaucoma, rather than any excessive formation or secretion of fluid into the eye. The success of surgical or medical treatment appears at present to depend principally on improvement in the facility of outflow of aqueous humor from the eye.

Findings in the screening for glaucoma conducted by the Philadelphia Committee for Prevention of Blindness of more than 10,000 persons between the ages of 40 and

65, employed in various industries, was reported by Dr. Solomon S. Brav and Dr. H. Peter Kirber. On the basis of their work, they advocated the practice of tonometry on all persons over 40 years of age and observation over a long period of all patients with borderline glaucoma.

Rheumatoid nodules of the eye were studied both clinically and histologically by Dr. Everett L. Goar, of Houston, Texas. Cases of this type are rare, and the ocular lesions have not been more amenable to treatment than systemic disturbances in rheumatoid arthritis. However, if corticotrophin (ACTH) and cortisone are given early in the course of the disease, and before the rheumatoid nodules become excessively large, these agents may stop the progress of the ocular lesions and prevent blindness.

Dr. Arthur A. Siniscal, of Rolla, Mo., has tested the effects in trachoma of the various sulfonamides and antibiotics at the Missouri Trachoma Hospital during the decade from 1941 to 1951. In his experience, the antibiotics do not have any specifice effect on trachoma per se but are of value in clearing the secondary infections associated with this disease. The sulfonamides remain as first choice in the treatment of trachoma at the present time, and the newer, highly soluble, nontoxic salts are especially effective.

Dr. Charles L. Schepens, of Boston, director of the clinic on retinal detachment at the Massachusetts Eye and Ear Infirmary, discussed the value of careful examination of the periphery of the fundus in search for tears in the retina or lesions indicating subclinical retinal detachment. The diagnosis is aided by scleral depression by an instrument that pushes the periphery of the fundus in view with the ophthalmoscope.

Results of an investigation of the microscopic and submicroscopic structure of the vitreous body, in ox eyes and human eyes, were reported by Dr. Antonio Grignolo, of Parma, Italy. He demonstrated by the use of lantern slides the structural formation existing in the vitreous, showing that it is not a structureless gel. The vitreous contains real fibers, visible with the phase microscope; and examination with the electromicroscope reveals the presence of a submicroscopic fibrous structure.

The influence of corticotrophin on the course of retrolental fibroplasia was studied in the Babies Hospital and the Lincoln Hospital of New York, and reported by Drs. A. B. Reese, F. C. Blodi, William A. Silverman, John C. Locke, and Richard L. Day. The studies were carried out on all premature infants in these hospitals in whom retrolental fibroplasia was thought to be developing. The method of treatment was to give 15 mg. per kilogram of body weight daily for two to three weeks. The findings indicated that the treatment should not be carried on longer than two weeks. About two of three of the patients treated showed improvement, but the results of the treatment are not conclusive.

## NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

**R. Townley Paton, M.D., *Chairman***

**Raymond L. Pfeiffer, M.D., *Secretary***

***Regular Meeting, May 21, 1951***

### CLINICAL PRESENTATIONS

**New Procedures in Lateral Canthus Surgery.** DR. DANIEL B. KIRBY. Two new procedures were presented.

1. A modification of the Wheeler canthoplasty for narrowing and shortening of the palpebral fissure when it is widened and elongated in cases of exophthalmos due to increased orbital volume in thyroid disease. Dr. Kirby stated that he retains

the lash line on the upper eyelid instead of removing it and always transplants the tongue of tarsal tissue from the lower to the upper lid. This, in addition to retaining the acute canthal angle, as Wheeler has done, gives a better profile, the baldness of the forward-placed canthus being avoided. When the correction requires quite a forward placement of the canthus, which covers the pupil on lateral excursions of the globe, to the embarrassment of the patient, it is necessary to resect and advance the lateral canthal ligament and place the canthus more laterally.

2. The development of a new principle and method of correction of so-called senile spastic entropion. The condition is recognized by Dr. Kirby as the result of the process of senile degeneration of the tissues of the eyelid, permitting the normal action of the orbicularis to flip or roll the flabby tarsus inward with the lashes against the globe. The proof of the principle and the denial of the spasticity of the orbicularis as the principal cause lie in the correction of the condition by resecting the tarsal tissue at its lateral border, then transplanting a tongue of tarsal tissue denuded of epithelium into a sheath at the lateral canthus at the original level and into, or just anterior to, the lateral tarsal ligament. The procedure has been successfully applied for nearly 15 years, but the author had just got around to making this preliminary report.

**What Does the Color-Blind Person See?** A Report on Monocular Blindness. Dr. Martin Bodian, Brooklyn (by invitation).

A review of the literature on monocular color blindness indicates its rarity. The few cases reported, while of great interest, fail to answer many important questions. Even the type of color blindness is omitted in some reports.

A case is reported in which the patient had a pronounced defect of green-blue vision in the right eye and "low discrimination" in the left eye. Because the color-perception defects of the left eye were so much slighter than those of the right eye, a comparison of the two eyes was considered worth while. In a test, using colored yarns, the right eye showed many more defects in color perception than the left eye. The latter made no errors with this test. The findings for each eye are tabulated.

Since at present there is no group of color tests that is infallible, no single test should be discarded. The Holmgren wools, though considered unreliable, were of definite help in examining this patient.

Unequal color vision in the two eyes may possibly be a cause of fusion difficulty and asthenopia.

Colored visual-field tests of color-blind subjects may produce bizarre and incomprehensible patterns. Lack of saturation of a given color will tend to produce a field similar to that for the same white object. This is noted for central, as well as for peripheral, fields. Even though it is admitted that white objects are far more practical for routine field testing, colored objects may shed light on visual function.

**Pathological Complications Following Intraocular Surgery.** Dr. Brittain F. Payne.

Examination of preparations of the eye in the laboratory offers valuable evidence concerning the failure of various intraocular operations. A microscopic study often shows certain technical errors, which may be corrected in future operations. In many cases microscopic examinations will determine conditions existing before the operation and account for the loss of the eye.

A review of the globes enucleated after intraocular operations at the New York Eye and Ear Infirmary revealed that loss of eyes after surgical procedures for glaucoma exceeded that of all other operative procedures combined. Enucleations after cataract extractions, removal of intraocular foreign bodies, and retinal-detachment operations followed, in about that order.

In a previous report (Operative Failures for Chronic Simple Glaucoma, *Am. J. Ophth.* 31:965 [Aug.] 1948.), at least three characteristics were shown to accompany the removal of the eyes for glaucoma: adhesions of the iris and cornea, closure of filtration channels by fibrosis, and inflammation of the uvea. These conditions hold true for the group of cases reported.

Loss of the eye after cataract extraction was characterized by inflammation of the uvea, reaction to retained lens substance, or downgrowths of epithelium.

Enucleations following the removal of intraocular foreign bodies were performed because of inflammatory changes, danger of sympathetic inflammation, and impregnation of ocular tissues with salts of heavy metals.

Most of the specimens after unsuccessful operations for retinal detachment showed the usual signs of atrophy and exhibited various degrees of inflammatory reaction, which necessitated the removal of the globe.

Ocular specimens treated by cycloelectrolysis and cyclodiathermy were submitted in this report, and one case in which retinal detachment was treated by diathermy, and later by a vitreous implant, was reported.

In order to review briefly the normal surgical relations of the iris angle and the limbus, as well as the area beneath the attachment of the rectus muscles, two specimens were presented. The eyes were removed for intraocular neoplasms, one tumor affecting the choroid in the region of the optic nerve, and the other, the optic nerve itself. Otherwise, the specimens were normal.

The first specimen, with a melanoma of the optic nerve, was normal in size and shape and presented a normal anterior chamber without dilatation of the pupil. It exhibited a normal iris angle and showed the extent of Descemet's membrane with reference to the external sulcus. This is important because in this region the surgeon often makes his incision in Descemet's membrane, rather than at the iris angle proper. Such an incision causes a curling of Descemet's membrane and sometimes permits fluid to enter the stroma of the cornea, causing it to become opaque and inflamed. From this specimen, it will be seen that the incision for either cataract extraction or operation for glaucoma should be in the true angle of the iris and is limited to an area 1 mm. in depth. This specimen also showed the long ciliary nerve penetrating the scleral tunic in an oblique direction to reach the perichoroidal space in the region of the ora serrata. This area is frequently disregarded by surgeons in diathermy operations for detachment of the retina. If the long ciliary nerve is injured or the ciliary artery is punctured by a diathermy pin, the globe may suffer innervational disturbances on that side or hemorrhage, which may prevent reattachment of the retina.

The second specimen, which exhibited an intraocular neoplasm in the region of the optic nerve with a normal anterior segment, showed the pupil dilated by atropine, with a consequent change in the depth of the anterior chamber. Obviously, an incision at the limbus in a patient with a dilated pupil will require greater technical skill than was exhibited in the operation on the preceding eye. This may explain the reason for injuries to the iris in cataract incisions with a Graefe knife when the pupil is widely dilated.

*Glaucoma.*—The first specimen was that of a woman aged 82, with the final clinical diagnosis of absolute glaucoma of the right eye. Cycloelectrolysis was performed on the right eye in June, 1950. The tension was not relieved, and after some weeks an iris inclusion was performed. After considerable treatment and expectant observation, the eye failed to improve and became inflamed and red, and the patient requested its removal because of intense pain and blindness.

The second globe was hyperopic in type and exhibited a shallow anterior chamber and a swollen lens capsule with an inclusion of the iris in a corneal wound. The ciliary body on the side of the wound showed considerable inflammatory and degenerative reaction as a result of cycloelectrolysis. There was atrophy of the ciliary muscle with inflammatory proliferation of the pigment epithelium. Obviously, there was no relief of the increased pressure, and enucleation was the operation of choice.

A third specimen, somewhat elongated and showing an almost complete anterior staphyloma with aphakia, was presented. Iridocorneosclerectomy, followed by cycloelectrolysis two years later, failed to resolve the tension, and the eye was eventually lost. From the microscopic appearance of the specimen, it seemed that little was to be gained from the cycloelectrolysis, and the eye hardly offered a favorable field for such an operation. The specimen revealed true glaucomatous cupping of the nerve with atrophy and complete anterior synechias, with remains of the crystalline lens in the periphery and internal to the ciliary body on either side. There were definite atrophy and some proliferation of the pigment epithelium of the ciliary body. The cycloelectrolysis was undoubtedly performed in an effort to retain the eye, and it is doubtful whether there was much hope of its success.

The failure of cyclodialysis and discission following a cataract extraction in 1946 is shown in the eye of a woman aged 71, from one of the services at the New York Eye and Ear Infirmary.

The section exhibited a globe which was somewhat shorter than normal in the anteroposterior diameter. The pupil was dilated; the anterior chamber was shallow, and the crystalline lens had been removed. Evidence of a corneal incision could be seen on one side, with the iris adherent to it. Both the iris and the ciliary body were more inflamed than the two preceding sections. Therefore it might be said that cyclodiathermy for glaucoma may cause more inflammatory reaction than cycloelectrolysis.

The next specimen was illustrated by two sections with conventional stains. The globe was that of an elderly woman who had had occlusion of the central retinal artery about six months before the enucleation was performed. Anterior uveitis and secondary glaucoma developed. An operation was performed at her request in order that the eye might be retained if possible. A generous anterior sclerectomy was performed with inclusion of the iris. The specimen showed a shallow anterior chamber with dislocation of the crystalline lens and its impingement on the anterior margin of the operative wound. A vitreous hemorrhage was present, and strands of vitreous were seen in the filtering wound. Obviously, the operation failed to preserve filtration, and the futility of such operations after vascular accidents of this type is demonstrated.

A globe removed after an unsuccessful trephine operation showed complete anterior dislocation of the crystalline lens, with its equator included in the filtration wound. An intraocular hemorrhage had occurred previously, signs of which remained in the vitreous and the subretinal space in the region of the macula.

Sections of a globe showing a clean iridectomy with a good filtration scar illustrated a successful type of operation. The eye was finally enucleated because of the presence of a neoplasm in the posterior portion of the globe. The patient had been under treatment with myotics for a long time, and a clear view of the fundus could not be had until the iridectomy was performed. After the operation the surgeon was able to see a mass in the choroid and, fearing it might be a malignant neoplasm, decided to remove the eye. Microscopic examination revealed angiomatosis of the choroid.

*Juvenile Glaucoma.*—The next five sections were presented to illustrate the failure of various operations performed for the relief of glaucoma in infants and children. The term "juvenile glaucoma" should be applied to the conditions commonly called buphthalmos and hydrophthalmos and should include all cases of increased intraocular tension in children up to the age of 15 years.

Buphthalmos is a descriptive term, often confused in textbooks and articles with hydrophthalmos and referring to generalized enlargement of the globe from increased intraocular pressure. Until a better term is accepted, buphthalmos may be described as a glaucomatous condition in which the anterior chamber is compressed or absent as a result of broad adhesions of the iris to the corneal endothelium. Buphthalmic conditions react unfavorably to all medical and surgical procedures.

Hydrophthalmos is characterized by a deep anterior chamber, a wide angle of the iris, deficiency of the ligamentum pectinatum, or absence of Schlemm's canal. The iris is usually thin and atrophic, and the lens is relatively small and often partially or completely dislocated. Hydrophthalmos is somewhat amenable to treatment and may respond to surgical measures for the preservation of some useful vision.

The first section represented the eye of a child aged 10 years, clinical diagnosis being congenital glaucoma in both eyes. The right eye was more involved than the left and was greatly enlarged. Cyclodialysis, performed on the right eye in 1943, maintained the tension and preserved some sight. Owing to exposure of the cornea, lid adhesions were made in 1947, but two years later pain, irritation, and blindness led to enucleation of the eye. Examination of the specimen showed a typically enlarged eye with a deep anterior chamber and a fairly well-preserved crystalline lens. The fibrous tunic was especially distended anteroposteriorly, and the iris was atrophic, with a deficient drainage angle.

The next two specimens were sections of the right and left eyes, respectively, of a girl, aged 6 years, with enlarged globes since birth and a history of ophthalmia neonatorum. Iridectomy was performed on both eyes, and the right eye ruptured just prior to enucleation. The enucleations were performed at the same time, because of extreme pain, blindness, and failure of the iridectomies. Examination of the left globe gave essentially the same microscopic picture as that presented in the preceding specimens. The globe was enlarged; the ciliary body was detached as a result of "artefact"; the lens was in place, but the iris showed atrophy and defects at its drainage angle. The right eye showed abscess of the cornea with albuminous fluid in the anterior chamber and complete detachment of the retina and choroid by massive hemorrhage.

Two other sections were submitted to illustrate cases of buphthalmos. The first slide showed an enlarged globe with an extremely thin fibrous tunic. The outline of the crystalline lens was represented by a thin rim of cortex in the capsule. The iris was closely applied to the posterior surface of the cornea and was included in a complete staphyloma. Portions of the iris were attached also to the anterior surface of the crystalline lens. The optic nerve showed pathological excavation. There was no evidence of an anterior chamber in this specimen, and the condition conformed to the definition of buphthalmos.

The second preparation illustrating buphthalmos showed almost complete absence of the anterior chamber with anterior synechias including the greater portion of the iris. The crystalline lens remained in place, and the optic nerve was pathologically excavated, but the fibrous tunic was less distended than in the first specimen.

*Eyes Removed After Cataract Operations.*—A patient aged 44 gave a history of having been struck in the right eye with a stone at the age of 10 years. A cataract operation was performed five years later, with some restoration of sight and about two years before enucleation the eye became irritated and red and the patient requested removal of the eye for the relief of pain. Examination of the globe showed secondary glaucoma, a shallow anterior chamber, and pathological depression of the optic nerve. The iris was adherent to a corneal wound, and vitreous extended between two islands of lens substance.

A patient aged 46 had several operations, including a cyclodialysis, after intracapsular cataract extraction. The specimen demonstrated a downgrowth of epithelium, which extended across the pupil and blocked the drainage angle of the iris. The progress notes in this case failed to indicate the interval before a downgrowth of epithelium was suspected.

The development of typical secondary glaucoma following the incomplete removal of lens substance in a cataract operation was shown in the next specimen. The patient had a massive intraocular hemorrhage, which could not be transilluminated clearly, and, owing to pain and lack of vision, the eye was removed.

The specimen showed a widely dilated pupil and a deep anterior chamber with remains of the crystalline lens back of the iris. The retina was partially separated by hemorrhage, which seemed to have arisen in the central retinal vessels.

A patient aged 76 had a cataract extraction two months before enucleation. The specimen was characterized by retained lens substance, which had become acutely inflamed and exhibited complete detachment of the choroid. Evidently, the surgeon feared sympathetic ophthalmia and advised enucleation.

The last specimen of the postcataract series represented an inclusion cyst of the anterior chamber with a typical ring of Soemmerring. This downgrowth may have been caused by buckling of the epithelium of the limbus in the incision due to tight sutures. Several specimens have shown epithelium in the suture tracts, but this finding is not a consistent one.

*Intraocular Foreign Bodies.*—Two slides were shown from a case of retained intraocular foreign body in the scleral tunic. The first slide, stained by the conventional hematoxylin-eosin method, showed the foreign body embedded in the fibrous tunic, without much reaction in the rest of the eye. The second slide was prepared by Perls's stain, by which siderosis bulbi was readily demonstrated by the reaction of the epithelium to the stain. This eye was submitted to the laboratory from outside sources without a definite history. Evidently the surgeon saw sufficient clinical evidence for its removal.

The fate of an eye after a successful removal of an intraocular foreign body by the posterior route is exemplified in the following cases. A man consulted me in May, 1949, stating that his eye had been inflamed and red for three days. Examination showed a pronounced ciliary blush with a small opening in the midportion of the iris, just temporal to the pupil. Because an intraocular foreign body was suspected, localization by means of the x-ray was ordered. The foreign body was found in the posterior portion of the globe, and the patient remembered that he had broken some cement with a hammer about three months before. The foreign body was removed successfully, and the patient's vision improved from 20/50 to 20/30, and he was discharged from the hospital with little or no irritation of the eye. He disappeared and was not seen until Sept. 11, 1950; at that time his eye was painful and red, and the pupil was contracted and cloudy. Light perception was absent, and the question of sympathetic ophthalmia arose. Enucleation was performed in October, 1950. Examination of the globe showed definite secondary glaucoma, iridocyclitis (subacute), cyclitic membrane, and detachment of the retina. The most startling finding was that of the crystalline lens in the region of the optic nerve. Although the capsule was ruptured, the lens was fairly well preserved. An intense "foreign-body reaction" was present around the lens, and the beginning formation of a fibrous bed was evident.

*Enucleation Following Retinal Detachments.*—Operations for retinal detachment following cataract extractions are often unsuccessful, as illustrated by the specimen in a case of cataract extraction six months before, in another hospital. The eye was subsequently operated on for retinal detachment but did not respond and became inflamed and blind. The eye was enucleated at the Infirmary for fear sympathetic ophthalmia might develop. Examination of the specimen in the laboratory showed beginning atrophy of the globe with complete detachment and degeneration of the retina and a suggestion of retinitis proliferans. Remains of the crystalline lens and vitreous were seen in the pupillary area, and the iris and ciliary body were inflamed.

Three sections were shown from the eye of a patient who received diathermy for retinal detachment, with later development of cataract. The cataract was extracted, but the retina again became detached. A second diathermy was performed, and a vitreous transplantation was made at this operation. The eye responded poorly and was enucleated owing to an inflammatory reaction. A careful examination of the section showed beginning atrophy with complete detachment of the retina. Evidence of a diathermy puncture of the long ciliary nerve on one

side was shown in several of the sections. It is entirely possible that the cataract developed after injury to the long ciliary nerve. The vitreous transplant could not be detected by microscopic examinations. Considerable diffuse inflammation was present in the globe, accounting for its removal. Although most surgeons appreciate, and take into account, the anatomical relations when operating, it is entirely possible that the long ciliary nerves and vortex veins are frequently forgotten in operations for retinal detachment.

*Conclusions.*—An attempt was made to show some of the causes of failures of various intraocular operations.

Cycloelectrolysis and cyclodiathermy for glaucoma need further investigation before definite opinions can be given as to their efficiency. Conventional operations for glaucoma fail for various reasons.

Cataract operations may be complicated by downgrowths of epithelium, development of secondary glaucoma, and iridocyclitis.

An eye removed after extraction of an intraocular foreign body usually undergoes atrophic changes or is impregnated with metallic salts, creating chronic irritation.

Operations for retinal detachment may be hampered by careless appreciation of anatomical markings. Injury to the long ciliary nerves and vortex veins is cited as an example.

Finally, a good surgeon always follows his case to the bitter end, and that means a study of the specimen in the laboratory.

**Hereditary Clues in the Etiology and Treatment of Strabismus.** Dr. Abraham Schlossman (by invitation) and Dr. Bruno S. Priestly (by invitation).

Of 158 patients with strabismus observed at the department of motor anomalies of the New York Eye and Ear Infirmary, 75, or 47.5%, belonged to families with two or more members affected with squint. It was stated that in convergent strabismus, hypermetropia alone is not the cause of the squint, and the other factors which may play a role were evaluated. Hyperactivity of the center of convergence, which responds excessively to any degree of accommodational effort; defective fusion faculty, and obvious anatomic malformations, although important, were not the major inherited factors except in a small percentage of the families. The direction (convergent or divergent) of squint was always the same in all but six of the 86 families; yet the type of squint varied a great deal in the same family. Any theory of the origin of squint must be broad enough to embrace these facts. There are probably at least two types of inheritance. In the one group, the defect is in the ectoderm and involves the nerve tissues, whereas in the other the mesoderm is defective and the muscles, check ligaments, etc., may be abnormal.

The mode of inheritance is recessive.

By examining his parent, it is sometimes possible for the physician to foretell what the future holds in store for the patient if he should remain untreated. In the surgical management of strabismus, the behavior of the squint in one member of the family may serve as a fair guide to the response of another member to similar operation if the types of strabismus are the same in the two members. Two cases of surgical overcorrection in two members of the same family were discussed. One case was that of a mother and son with similar types of convergent strabismus, while the other concerned identical twins. In the third case, that of a child with 65Δ of strabismus, only one muscle was operated on as a first procedure, because his mother's squint had been overcorrected; 45Δ was corrected by this procedure.

# News and Notes

EDITED BY DR. W. L. BENEDICT

## GENERAL NEWS

**Medical Motion Pictures.**—A revised catalogue of motion pictures available through the Committee on Medical Motion Pictures of the American Medical Association is now ready. Copies will be sent to the secretary of each county and state medical society. This catalogue lists 62 16-mm. films, most of which are at the professional level. Fourteen of these films are suitable for showing to lay groups. Eight new films have been added. Copies are available upon request from the Committee on Medical Motion Pictures, American Medical Association, 535 No. Dearborn St., Chicago 10.

## SOCIETY NEWS

**Société française d'ophthalmologie.**—The 58th Congress of this society was held in Paris, May 6 to 10, 1951, and it was, as usual, a very international meeting, which is natural, since half the membership of the Society is non-French. Dr. Bernard Samuels, of New York, and Dr. Henry Hill, of Maine, were the only Americans attending.

The principal paper, "Rapport," by Dr. Guy Offret, of Paris, was on "The Primary Tumors of the Orbit." It is impossible to review in a few lines this comprehensive piece of work. It is now published as a separate volume of over 400 pages, obtainable by applying to the treasurer of the French Society, Dr. Jacques Bruneau, 28 rue Vignon, Paris 9. On Tuesday, May 8, during all of the morning and most of the afternoon, the topic was discussed by over 20 members. All the aspects were touched upon—clinical, pathological, and surgical.

Forty other papers were read on the four other mornings: (these are to be published in the volume of *Transactions,* which will come out toward the end of the year and can also be obtained from the Treasurer). Sunday was devoted to cataract. J. Gallois (Paris) stated the belief that sodium iodide has a favorable effect on incipient cataract. His paper was followed by a lively discussion on the pros and cons of the medical treatment of lens opacities, the general impression being that efficient medical handling will necessitate further knowledge of the chemistry of the normal and the opaque lens. G. Jayle and Jacquenoud (Marseilles) gave a favorable report on the use of general anesthesia in cataract extraction, but the discussion showed that this method was not generally accepted. J. Babel (Geneva) spoke on experimental cataract (alloxanic) and its relation to diabetic cataract. J. Nordmann and L. Dillschneider (Strasbourg) spoke on carbohydrate metabolism of the lens; they believed that it is important, for when it is inhibited by glyceraldehyde a cataract always forms. J. Zanen and A. Meunier (Brussels) read a paper on retrolental fibroplasia, with the report of a personal case in identical twins, all four eyes being affected. L. Paufique and H. Chavanne (Lyons) published statistical results in a series of cataract extractions when the first eye had already been lost. They advocated preliminary iridectomy two months before performing the extraction. A. Franceschetti and J. Rickly (Geneva) read a paper on a case of posterior lenticonus which had been difficult to differentiate from a cyst on account of its being laterally located. G. Jayle and A. Ourgaud (Marseilles) discussed the relation of secondary detachment to intracapsular and extracapsular cataract extraction. Many others gave their opinion, and on the whole it was felt that detachments were not more frequent after the intracapsular extraction and that should a detachment occur the final operative results were more favorable after an intracapsular extraction, since the periphery of the retina was better visualized. G.

Sourdille criticized the extreme length of time entailed by certain techniques; he uses sutures but believes that complicated ones do more harm than good; he prefers the Graefe knife to the keratome and scissors. G. Renard and Laporte (Paris) gave the history of a child who, together with several malformations, had crystals in both lenses. G. Jayle, A. Ourgaud, and P. Berard (Marseilles) stressed the frequency, but favorable prognosis, of choroidal detachment after cataract extraction.

On Monday, the papers dealt with the conjunctiva, cornea, and sclera. J. van Manen (The Hague) had observed many fistulas, after corneal ulcers, during his practice in Indonesia. He gave a description of his operative technique, namely, conjunctival covering and a filtrating operation. J. Winkelman (Amsterdam) had experimentally transplanted scleral tissue into the rabbit cornea; the transplant cleared remarkably and pathological examination showed that scleral fibers had changed into corneal fibers. J. Mawas (Paris) stressed the considerable number of nerve endings in the cornea, this having important clinical consequences. A. Rollin (Paris) demonstrated an improved trephine for corneal transplantation. L. Paufique (Lyons) mentioned several technical improvements which made for better results in keratoplasty, in particular the use of beta radiation and cortisone against neovascularization. J. Doggart (London) read an interesting paper on the diagnosis and prognosis of Fuchs's epithelial dystrophy. Irritating medications should be avoided, as well as the frequent use of the tonometer.

M. Amsler (Zurich) spoke on keratoconus and stressed the frequency of early stages, which can be recognized only by keratography. Vermès and G. Offret (Paris) were able to examine the histopathologic changes in the cornea in two cases (father and daughter) of hereditary corneal dystrophy. A. Busacca (Saõ Paulo) gave his classification of corneal lesions based on both biomicroscopy and histopathology. J. Sédan, G. Farnarier, and G. Sobrepère (Marseilles) had noted, in many cases of influenzal conjunctivitis, small peripheral corneal ulcers, these probably being caused by previous trachoma or a simultaneous pathological nasal condition. P. Bierent (Sura) observed several cases of central corneal ulcers in which pellagra was the real cause.

On Wednesday, papers were devoted to the orbit and the adnexa of the eye. R. Nataf, P. Delon, and J. Chevassus (Tunis) used vital coloration to study, with the slit lamp, the lymphatic vessels of the conjunctiva. P. Desvignes and Brun (Paris) advocated an intracranial approach in most cases of frontal mucocele. D. Sabladini (Milan) reported a case of tuberculosis of the lacrimal gland in which no caseation was found and the granulomas were micronodules. A. Huber (Zurich) spoke on the diagnosis of orbital and cavernous angiomas. B. Strampelli (Rome) advocated a prosthesis with a curved posterior appendix which hooks into a tunnel lined with a mucous membrane transplant from the mouth. M. Alvaro (Saõ Paulo) discussed the various types of implants after enucleation; his personal choice was a plastic sphere covered with tantalum mesh. E. Wolff (London) discussed the pathology of xanthelasma, which derives from unicellar sebaceous glands found in the basal layer of the epidermis. C. Dejean and C. Boudet advocated x-rays for the diagnosis of varicose veins in the orbit. A. Larmante and M. Toulant (Algiers) remarked on the frequency of orbital tumors in children.

Thursday was for "free papers." P. Halbrón and Paquet (Paris) advocated surgical and orthoptic treatment for the complete cure of paralytic squint. I. Stankovic (Belgrade) reported on three cases of rete mirabile of the vitreous, this rare lesion probably being due to biochemical factors. F. Thiebaut and N. Matavulj (Paris) described an abnormal synkinesia (clonic convergence spasm). Calmettes, Deodati, and Amalric (Toulouse) stated the belief that Descemet's membrane can easily be injured in intraocular surgical procedures, particularly cyclodialysis. H. Miller, M. Levy, and M. Sapir (Paris) made a study of the diastolic retinal pressure in 84 cases of sympathectomy for hyperpiesis. L. Paufique and Hugonier (Lyons) described a new technique of scleral resection, in cases of detached retina, in which only one-half or two-thirds of the thickness of the sclera is removed.

J. Voisin (Paris) published the history of a child of 10 years, with conjunctival follicles and glandular reaction, which appeared due to the lymphoreticulosis recently recognized as usually inoculated by the scratches of a cat. H. and R. Rossano (Paris) reported on a new visual acuity chart for children; they stressed the difficulty of testing the visual acuity alone, and not the perception. L. Ferrata (Milan) and G. Calamandrei (Florence) reported on their experience with corticotropin (ACTH) in ophthalmology; there was nothing unusual in their report, except that they used a purified extract, allowing doses of about one-tenth those generally necessary. A. Fritz (Brussels) advocated the use of new contact lenses only 0.2 mm. thick.

On Monday afternoon, M. Alaerts (Brussels) gave a most interesting lecture on the myopia of the Medicis, which he traced through three centuries. On Monday and Wednesday afternoons there were operative sessions in most of the Paris hospitals. Tuesday afternoon was devoted, as usual, to a visit to one of the artistic buildings in the neighborhood of Paris. This year the members visited the Palace of Fontainebleau.

On Monday evening, about 200 members and their wives dined together at the Cercle Interallié. The after-dinner speeches were by Prof. Binet, dean of the medical school, who presided; Mr. Law, of London; Mr. Weve, of Utrecht; Mr. Ehlers, of Copenhagen; Mr. Moutinho, of Lisbon, and the author of this review, as secretary-general of the French Society.

The 59th Congress will be held June 22 through 26, 1952.

EDWARD HARTMANN, M.D.

# Book Reviews

**Tumors of the Eye.** By Algernon B. Reese, M.D., D.Sc. (Hon.), F.A.C.S. Price,? Pp. 574, with 511 illustrations, 122 in full color. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 49 E. 33d St., New York 16, 1951.

This book is a comprehensive and authoritative treatise, which will be of very great value to ophthalmologists and pathologists. Dr. Reese has combined a detailed account of the pathology of ocular tumors with an analysis of their clinical course, richly illuminated by his own vast experience and embellished with sagacious comments in respect to differential diagnosis, surgical techniques, and other therapeutic procedures. The whole is set forth in a fluent and eminently readable text. The illustrations are excellent, and the publisher is to be complimented on the quality of the reproductions.

Dr. Reese is, naturally, at his best in those sections dealing with topics that have been the field of his original study in the past. His important contributions to the use of x-ray therapy in cases of bilateral retinoblastoma have been reported elsewhere. Here, for the first time, he is able to set out his views of this disease in full perspective. The frequency of the disease in siblings of afflicted children, he finds, is 1 out of 378. He does not hesitate, therefore, to advise healthy parents who have had one child with retinoblastoma to have more children. In regard to survivors of the disease who have reached parental age, the situation is radically different. I quote:

> . . . We have in our series of 190 patients with retinoblastoma, only 6 survivors with children. The children total 10, and 9 of these had bilateral retinoblastoma. This seems sufficiently impressive to interdict the bearing of progeny by all survivors of retinoblastoma.

In 1931, Reese reported on the incidence of optic-nerve invasion by retinoblastoma. The report was based on 119 eyes enucleated between 1878 and 1929. In 53% of the eyes the tumor extended into the optic nerve, and in 43%, beyond the point of section of the nerve. A second series, reported in 1948, of 116 eyes enucleated between 1934 and 1947, showed that the tumor extended into the optic nerve in only 27%, beyond the point of section in only 8.5%. The reduction in the incidence of optic-nerve extension is, no doubt, attributable to earlier diagnosis. Reese points out that in the majority of eyes from the earlier series the optic nerve was cut short, and in the majority of the eyes of the later series it was cut long. The tumor usually extends only a few millimeters up the nerve. The improved statistics are a brilliant tribute to Dr. Reese's influence in the institution from which the report was issued. Once the tumor has reached the place where the central vessels enter the nerve, it tends to spread to the meninges. Consequently, Dr. Reese believes that nothing is gained by a preliminary intracranial section of the optic nerve. On the contrary, he advises enucleation with a long stump of optic nerve, prompt histologic examination of the cut end of the nerve, and postoperative irradiation with radon seeds implanted into the apex of the orbit in those cases in which the cut end of the nerve contains tumor.

In more than a third of the cases of bilateral retinoblastoma in his series, the lesion in the second eye was not noted on first examination.

> . . . In every case in which the diagnosis of retinoblastoma has been made in one eye, the fellow eye should be examined thoroughly under ideal conditions, which are: general anesthesia, dilation of the pupil, use of a speculum for retraction of the lids, forceps with which to rotate the globe in all directions, and Ringer's solution with which to keep the cornea moist if necessary.

In cases of bilateral involvement the first eye should be enucleated, and the second also if it contains a tumor sufficiently large to have destroyed vision. Radiation therapy should be limited to the second eye, and to those cases only in which there is a chance of saving vision in that eye. Of 19 such patients who have been followed for five to 15 years, there were 12 living without recurrence, of whom 6 had vision and 6 were blind. Blindness is due chiefly to phthisis bulbi or to glaucoma. The complications of x-ray therapy are not negligible and are presented by Dr. Reese in detail.

Dr. Reese's contributions in the field of ocular melanomas are too numerous to mention here. He accepts Masson's conclusions that the nevus cell is derived from the Schwann cell. While Masson's evidence of the neural origin of the nevus cell is monumental, it is based exclusively on morphologic studies. Willier has shown that excision of a certain portion of the neural crest in chick embryos of appropriate age leads to the absence of pigment in the skin over a corresponding segment of the body. The nerves in the unpigmented zone are not devoid of Schwann cells. In this species, then, the skin melanoblasts are derived from the neural crest, but are independent of the Schwann cells. The matter is not purely academic, for acceptance of Masson's theory has led Reese to conclude that there are two genotypically distinct melanomas of the choroid, the "Schwannian type" and the "stromal type."

He cites the important work of Theobald, who showed that an appreciable fraction of the malignant melanomas of the choroid arise within the long ciliary nerves. It is well known, however, that these nerve bundles often include choroidal melanophores, and Reese himself points out that the orbital melanomas arising in the extraocular portion of these nerves are found only close to the eyeball, where melanophores of the choroidal type are also to be found.

The tumor which Reese designates as of "stromal type" is composed of cells many of which are heavily pigmented and have long branching processes, similar to the fully differentiated choroidal melanophore. This rare tumor has in the past been considered merely an extreme variant in cell type of choroidal melanomas. The assumption that this tumor is derived from a different cell of origin than the "Schwannian type" is unproved. Cells with branching processes, with or without pigment, are not infrequently to be found in mixed-cell tumors of the "Schwannian" group.

One would expect that a tumor showing such a high degree of differentiation in its cells as the "stromal type" would be less malignant than tumors in which the cells are more anaplastic. Reese has the impression that the stromal type is more malignant. Statistics on this point will be awaited with interest.

The section on vascular tumors has to be read in full to be appreciated. Dr. Reese has done a yeoman's job in differentiating the multifarious forms of these tumors. He writes in this field with the full authority of one who has studied the subject both widely and deeply. He has done more than anyone else in establishing the value of sclerosing solutions in the treatment of epibulbar tumors of this type. He presents in the text detailed discussion of the advantages and restrictions of this form of therapy.

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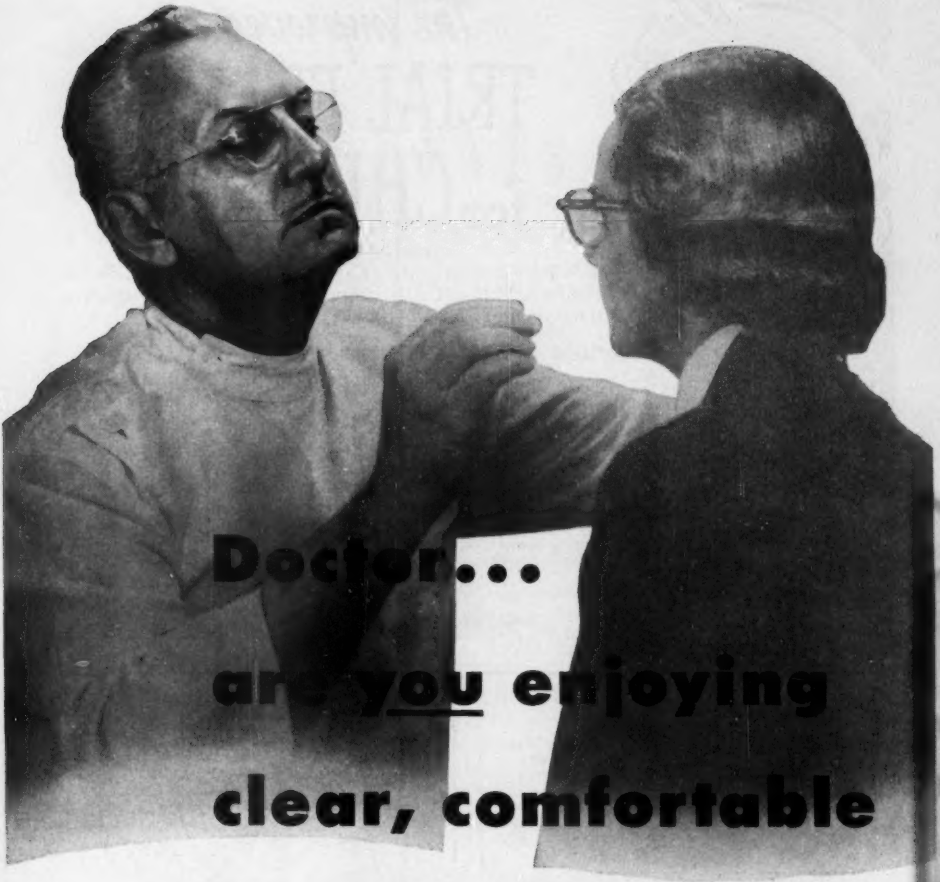

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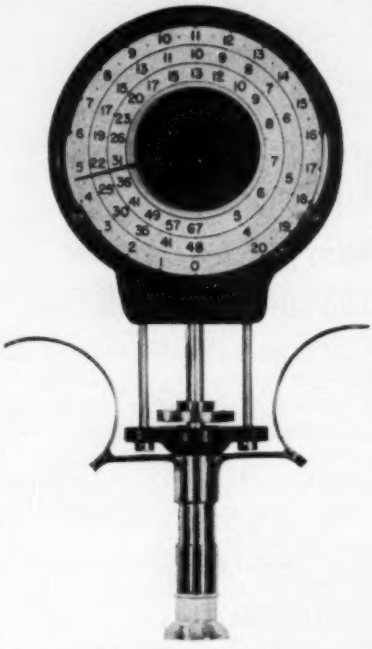

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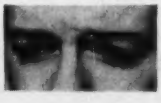
Some eyes can take it  . . . some eyes cannot!

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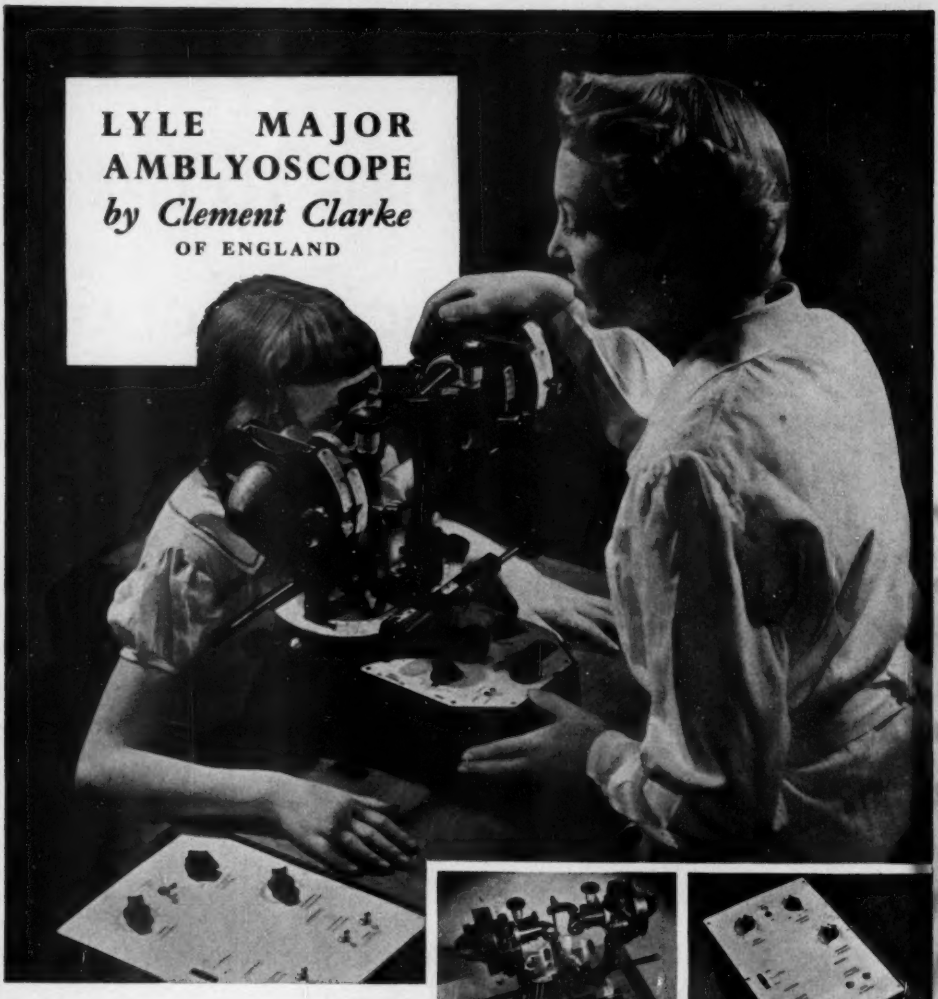

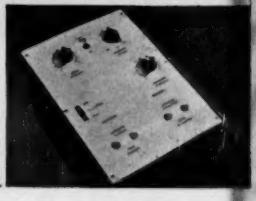

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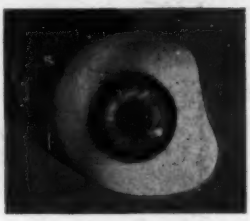

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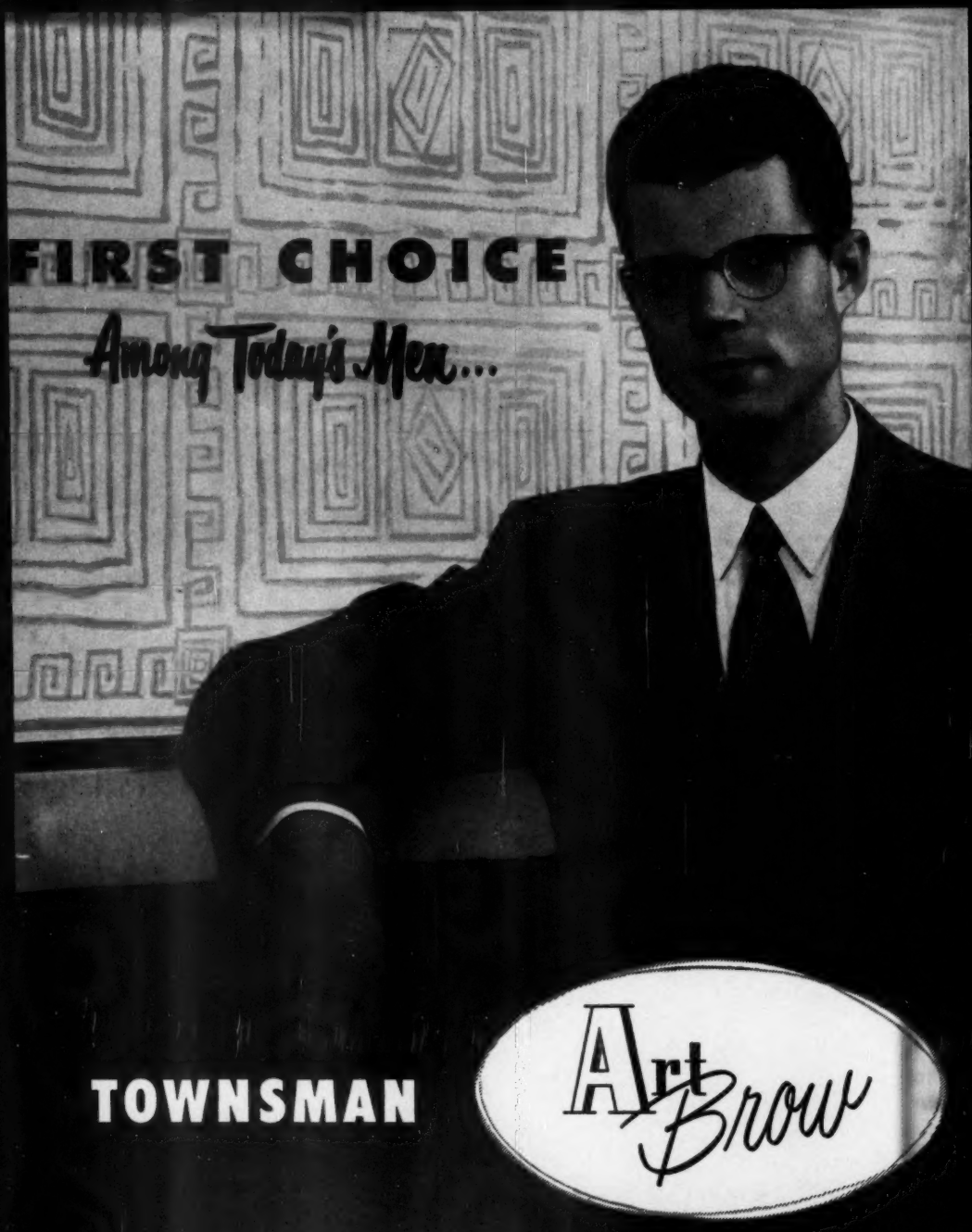


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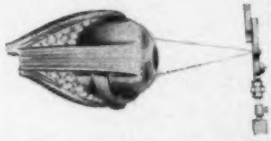

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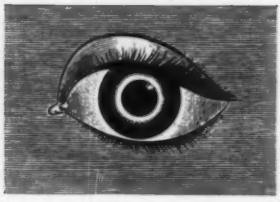

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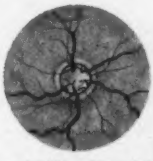

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